VOL. CLXXVIII, No. 4 OCTOBER, 1929 No. 691

OCT 7 1929

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

Medical Library

ESTABLISHED 1820

URINE FORMATION DURING THE ACUTE AND CHRONIC NEPHRITIS INDUCED BY URANIUM NITRATE. A CONSIDERATION OF THE FUNCTIONAL VALUE OF THE PROXIMAL CONVOLUTED TUBULE. By WILLIAM DEB. MACNIDER, M.D. . . . 449

WATERMELON-SEED EXTRACT IN THE TREATMENT OF HYPERTENSION. By T. L. ALTHAUSEN, M.D., and WM. J. KERR, M.D. 470

ACUTE LEUKEMIA: A REVIEW OF THE LITERATURE AND OF TWENTY-EIGHT NEW CASES. By STAFFORD L. WARREN, M.D. 490

SYSTEMIC RELAPSES DURING LIVER INDUCED HEMOPOIETIC REMISSIONS IN PERNICIOUS ANEMIA. By RAPHAEL ISAACS, M.D. 500

HEMORRHAGES FROM LACERATIONS OF THE CARDIAC ORIFICE OF THE STOMACH DUE TO VOMITING. By G. KENNETH MALLORY, M.D., and SOMA WEISS, M.D. . 506

THE PATHOGENICITY OF YEASTLIKE FUNGI ISOLATED FROM THE HUMAN GASTRO-INTESTINAL TRACT. By ROBERT N. NYE, M.D., LEON G. ZERFAS, M.D., and M. AGNES CORNWELL, A.B. 515

THE CEREBRAL CIRCULATION. IX. THE RELATIONSHIP OF THE CERVICAL SYMPATHETIC NERVES TO CEREBRAL BLOOD SUPPLY. By STANLEY COBB, M.D. . 528

LYMPHATIC ABSORPTION OF PARTICULATE MATTER THROUGH THE NORMAL AND THE PARALYZED DIAPHRAGM: AN EXPERIMENTAL STUDY. By WILLIS S. LEMON, M.D., and GEORGE M. HIGGINS, PH.D. 536

THYRONEURAL DYSTROPHY. THE ASSOCIATION OF CONGENITAL MYXEDEMA WITH MENTAL AND NEUROMUSCULAR DISORDERS. By WALTER M. KRAUS, A.M., M.D., SAMUEL BROCK, M.D., and PAUL SLOANE, M.D. 548

THE INTRAVENOUS USE OF GELATIN SOLUTION IN HEMORRHAGE: (AN EXPERIMENTAL STUDY.) By WILLIAM L. WOLFSON, M.D., F.A.C.S., and FRANK TELLER, B.S., M.D. 562

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 50

Contents continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1929, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

A New and Powerful Vasodilator

Pharmacologic investigation has demonstrated that acetylcholine opposes epinephrin at every point. It dilates the peripheral arteries and arterioles and has a selective vasodilator action in the limbs. Under ophthalmoscopic examination, it has been shown to have a dilative action on the retinal artery.

Acetylcholine is extremely powerful. With regard to effect on arterial pressure, it is 100,000 times as potent as choline but only three times as toxic. In 1 to 100,000 solution it excites the uterus of a guinea pig; 0.001 mg. lowers arterial tension in cats. Acetylcholine also stabilizes smooth muscle tone and, when injected prophylactically, prevents certain types of anaphylactic shock.

Loewi, Gautrelet and other physiologists have called it the vagal hormone, whose function is to dilate peripheral arteries.

Acécoline

Acécoline is acetylcholine hydrochloride stabilized to prevent deterioration, sterilized by tyndallization and sealed in ampules to protect it from moisture. In this form the preparation maintains its potency until used.

Samples

On request, a sample box containing 3 ampules of 0.1 Gm. Acécoline each with 3 ampules of doubly distilled water will be mailed with complete literature

Made in France

by

LABORATOIRES CHEVRETIN-LEMATTE
L. LEMATTE et G. BOINOT, PARIS

Sole Agents for the United States

ANGLO-FRENCH DRUG CO. (U. S. A.) Inc.
1270 Broadway **New York City**

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1929

ORIGINAL ARTICLES.

URINE FORMATION DURING THE ACUTE AND CHRONIC NEPHRITIS INDUCED BY URANIUM NITRATE. A CONSIDERATION OF THE FUNCTIONAL VALUE OF THE PROXIMAL CONVOLUTED TUBULE.*

By William deB. MacNider, M.D.,

KENAN RESEARCH PROFESSOR OF PHARMACOLOGY, THE LABORATORY OF PHARMACOLOGY, THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA.

The study of function in relation to structure is perhaps the oldest of the methods of physiologic inquiry. The employment of this method in the simplest organs and organisms has certain definite limitations, for by its use it becomes difficult to interrelate in terms of a balanced functional response of an organ as a whole the various activities of the histologic components of the structure. Furthermore, deductions obtained from this type of experimentation through reasoning from structure have of their nature to be inferential and can rarely assume absolute values. Even with this purposely minimized conception of the method's value, we do not have to go far into the past few years to appreciate the truths which it has established in regard to the thyroid gland through the researches of Marine,[1] in regard to brain cells in surgical shock and recuperation by Dolley,[2] in regard to the pancreas by Banting, Best and Macleod,[3] and in a recent one of these lectures by Aschoff[4] in regard to the kidney. When, however, this method which has been so abundantly fruitful in ascertaining the functions of other organs has been applied to the kidney the tendency has been to minimize the results obtained in a disproportionate fashion to their

* Harvey Society Lecture, 1928–1929.

minimization when secured from other organs. Such a skeptical attitude is to a certain extent justifiable. In the kidney of the higher animals there is not only such an intimate relationship between widely separated types of tissue which participate in a common function, but such a variation in the cytologic character of these units that it becomes difficult, if not impossible, at present, through injury to separate one from the other functionally. With such an appreciation of the difficulties which will be encountered and of the judiciousness which must be used in making inferential conclusions, I feel that as a result of over twenty years of continuous study certain estimates in terms of function can be made concerning the different elements of renal structure.

Uranium in the form of one of its salts is one of the oldest substances to be used to induce a renal injury either for the purpose of obtaining acute and chronic renal changes comparable to those developing in man, or for the purpose of inducing such changes and attempting to correlate the histologic findings with the renal functional response. In 1854 Leconte[5] first used uranium as a nephrotoxic agent. Much later than this Richter,[6] Chittenden and Hutchinson[7] and Chittenden and Lambeth[8] became interested in the action of uranium, and Wallace and Myers[9] investigated the ability of the substance to induce a glycosuria. Schirokauer[10] and Heineke and Myerstein[11] induced both severe vascular and epithelial injuries with it, and noticed the anasarca which followed its use. Christian,[12] Christian, Smith and Walker[13] and Christian and O'Hare[14] described in detail the renal epithelial injury, and also described the occurrence of hyalin droplets in the walls of the glomerular capillaries. Pearce[15] classed uranium along with the chromates as a substance which early in its action very largely localized its injury to the convoluted tubules. In several studies[16,17,18,19] from my laboratory the selective affinity of this substance for the tubular epithelium when used in dogs has been emphasized, and it has been furthermore pointed out that the age of the animal[20] determines in large measure the severity of the toxic response. Later than these observations studies were conducted in which it was shown that uranium induced a rapid reduction in the reserve alkali of the blood in normal animals,[21] in animals with a naturally acquired chronic nephritis[22] and that a protection against it could be established by the use of a weak alkaline solution or glucose.[23,24] The injury in such animals was largely confined to the convoluted tubules and the protection resulted in preserving to a greater or less extent the histologic structure of these cells. These observations were confirmed by Goto.[25] At a later period the work of Suzuki[26] and Mitamura[27] in Aschoff's laboratory gave exceptional emphasis to the specific localization of the nephrotoxic action of uranium and enabled them to formulate certain functional deductions during the acute injury.

The observations which are to follow have been obtained by rendering dogs acutely nephropathic by the use of one subcutaneous injection of 2 or 4 mg. of uranium nitrate per kilogram and attempting to correlate the histologic changes in the kidney during the acute nephritis, the stages of repair and over a period of four years after the animals had developed a chronic nephritis with certain functional expressions in the blood and urine. A number of these animals have effected by different histologic methods such degrees of renal repair that they either gave no evidence of a functional disturbance or such changes were slight in character. In such animals secondary injections of uranium have been used to ascertain its influence upon function when the cytologic basis for this restored function or functional improvement was again subjected to morphologic alteration by the use of uranium.

The evidence of renal functional depression during the acute and chronic nephritis and during periods of recovery have been obtained by studying the animals at various periods after they had been rendered pathologic and terminating the experiments when such changes in function had developed so far as to make it desirable to check a given expression of renal function with the changes then existing in the kidneys. The daily volume output of urine has been obtained, the amount of albumin in grams per liter and the relative number and character of the casts it contained have been noted.

Associated with these simple studies of the urine, the reserve alkali of the blood has been determined by the methods of Marriott[28] and van Slyke and Cullen[29] and the immediate functional value of the kidneys ascertained by the phenolsulphonephthalein test of Rowntree and Geraghty.[30] Evidence of persisting renal dysfunction as shown by retention has been obtained by estimating the degree of urea nitrogen retention by the method of Marshall[31] as modified by van Slyke and Cullen[32] and nonprotein nitrogen and creatinin by the methods of Folin and Wu.[33]

The animals were given 500 cc. of water daily by stomach tube and fed on a mixed diet of bread, butter, meat and milk. In order to regulate to some extent the severity of the acute nephritis, animals varying in age have been used. It was hoped to induce in the older group of animals a more severe nephritis with but slight evidence of repair and functional restoration, while in the younger groups of animals there might be obtained from the same dosage of the nephrotoxic agent a less intense acute nephritis which would lend itself to changes of repair with the development of a chronic diffuse renal injury. A total of 72 dogs have been used in the experiments. On the basis of the acute response of these animals, both anatomically and functionally, as well as in terms of their ability to completely recuperate functionally or repair the kidney to a functional state indicative of a chronic nephritis, they may be divided into four groups.

Group I is represented by 21 dogs which either died during the acute stage of the nephritic process or were killed at various intervals of it for purposes of study and functional correlation.

Group II comprises 15 dogs which after having developed a severe acute nephritis returned to a complete functional normal.

Group III is made up of 36 animals, which, after having developed an acute nephritis, failed to make a functional adjustment back to the normal, but were left with such changes in the kidneys and gave evidence of such functional alterations in the blood and urine that they have been classed as animals with a chronic nephritis.

The animals of Group IV, 41 in number, were given an acute nephritis by the use of 2 mg. of uranium per kilogram. After they had either completely recovered functionally or recovered with the development of a chronic nephritis they were given a second injection of 2 or 4 mg. of uranium and the functional reaction in connection with the changes in the kidney studied.

In discussing the results obtained in these groups of experiments, it should be kept in mind that the functional studies were not terminal observations. Such observations were made on the respective animals at frequent intervals, as changed functional states demanded a study in connection with the pathology of the kidney from the commencement of the acute nephritis until the animals had established their pathologic normals in terms of a chronic nephritis, or, in cases of recovery, through this process and through the secondary uranium injury in case a secondary intoxication was employed.

The dogs used in the first group were over seven years old. None of the animals survived the acute injury longer than fourteen days. From the commencement of the nephritis until its termination studies were made every other day or every third day of the functional disturbance in connection with the changes in the kidney. These studies have shown by the second day of the nephritis an increase in the output of urine over the 500 cc. of water intake, and the urine has contained from 1.2 to 6.8 gm. of albumin per liter with numerous granular casts. The maximum output of urine at such a time has been 1427 cc. The urine early in the nephritis contains glucose. With these changes in the volume output of urine there occurs a sudden reduction in the elimination of phenolsulphonephthalein to a trace or to a negative elimination in a two-hour period and an equally sharp reduction in the alkali reserve of the blood. The reduction has varied from the normal of 8.1 to 7.85. Usually within twenty-four hours retention of blood urea begins, and later nonprotein nitrogen and creatinin, which by the sixth to the tenth day of the nephritis has reached 150 mg. of urea, 216 mg. of nonprotein nitrogen and 5.3 mg. of creatinin. During such periods of retention there is no change in the elimination of phenolsulphonephthalein and no attempt at a restoration of the

reserve alkali of the blood. Usually by the eighth day the amount of albumin has diminished without any change in the character of the casts, and toward the termination of the nephritis the volume output of urine may or may not be reduced below the water intake of the animal. This has very largely depended upon whether or not the animals retained the water.

In this, as in other groups of animals, the functional observations other than the output of urine are expressions of the histologic changes in the kidneys within an hour of the animals' death. The severity of the changes in the convoluted tubule epithelium in animals with this type of response, in which there was no attempt at recovery, have shown some variation in the respective animals, depending upon the duration of the nephritic process. The glomerular changes, however, have not shown the same degree of structural alteration as the duration of the nephritis progressed. These structures after the commencement of the renal injury have shown capillaries distended with blood, and the capillary endothelium has appeared prominent with deeply staining nuclei. Thrombosis of the vessels has not occurred, and only in the late stages of the process have exudates of any type been observed in the subcapsular spaces. There has been no hyperplasia of the capsular epithelium and no evidence of glomerular or periglomerular connective-tissue formation. The epithelium of the convoluted tubules has shown the selective action of uranium by developing an edema and necrosis, which varies in degree with the duration of the injury. It has been impossible for me to say that only definite segments of this tubule were involved in the injury. On the contrary, I believe that other tubules participate to some extent in the uranium reaction. This is slight as contrasted with the proximal convoluted tubule injury, and may be due to factors other than the direct action of this nephrotoxic substance. The cells of the descending limb of Henle's loop rarely if ever show evidence of injury. In 4 of the animals in this group obtained for autopsy between the fourth and tenth day of the nephritis occasional mitotic and premitotic figures were found in the degenerating material of the convoluted tubules. These changes, indicative of an attempt at repair which failed, were not observed in animals after the tenth day of the injury.

The functional expression of these lesions consists in the animal becoming polyuric with an albuminous urine containing granular casts. If the intake of water could be maintained the dogs persisted for as long as fourteen days in a polyuric state, the formation of urine equalling or exceeding the water intake. In those animals in which fluid was not retained there was a reduction in urine formation below the water consumption which was not associated with structural degenerative changes in the glomeruli. Associated with these changes in the volume output of urine there developed a definite relationship between the severity of the injury to the epithelium

of the convoluted tubules and the elimination of phenolsulphonephthalein and the decrease in the reserve alkali of the blood. Soon after the commencement of this evidence of renal failure there occurs a progressive retention of urea nitrogen, nonprotein nitrogen and creatinin. No member of this group of animals showed any definite

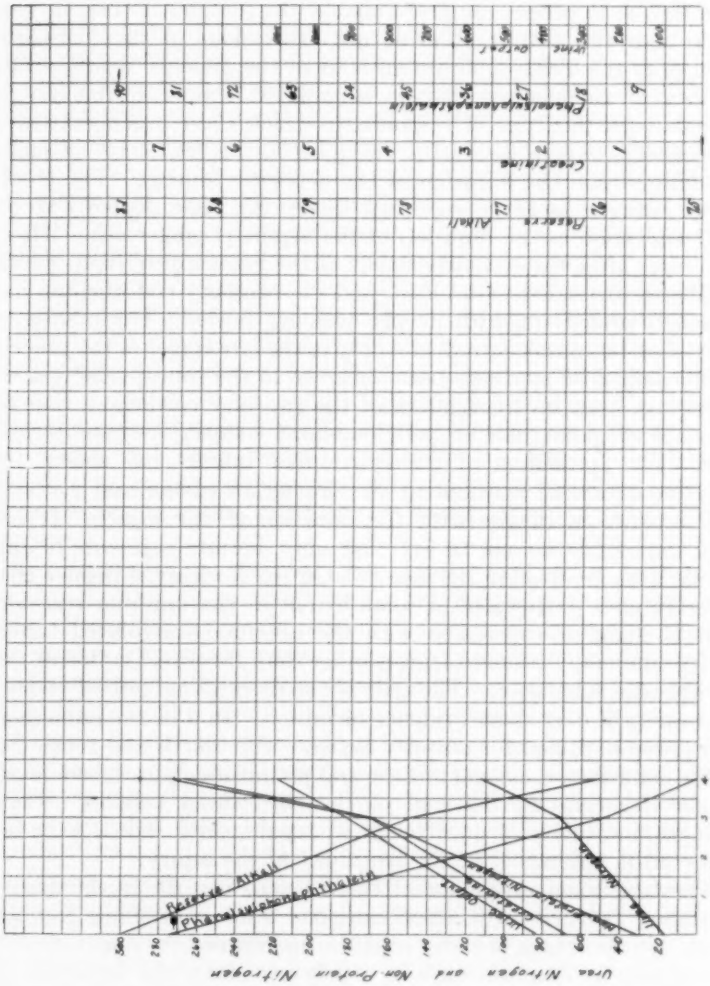


CHART I

evidence of tubular epithelial repair and in none was there any attempt at a restoration of renal function. (Charts I and II.)

A second group of animals of the series, but younger, between one and two years of age, were also given an acute nephritis by one subcutaneous injection of 4 mg. of uranium nitrate per kilogram and

subsequently studied in a manner identical with the first group. Fifteen of these dogs after developing an acute nephritis were able to effect such changes of repair to the kidneys that they returned to a functional normal. In this group it became necessary not only to study the acute changes, but, in addition, to study in correlation

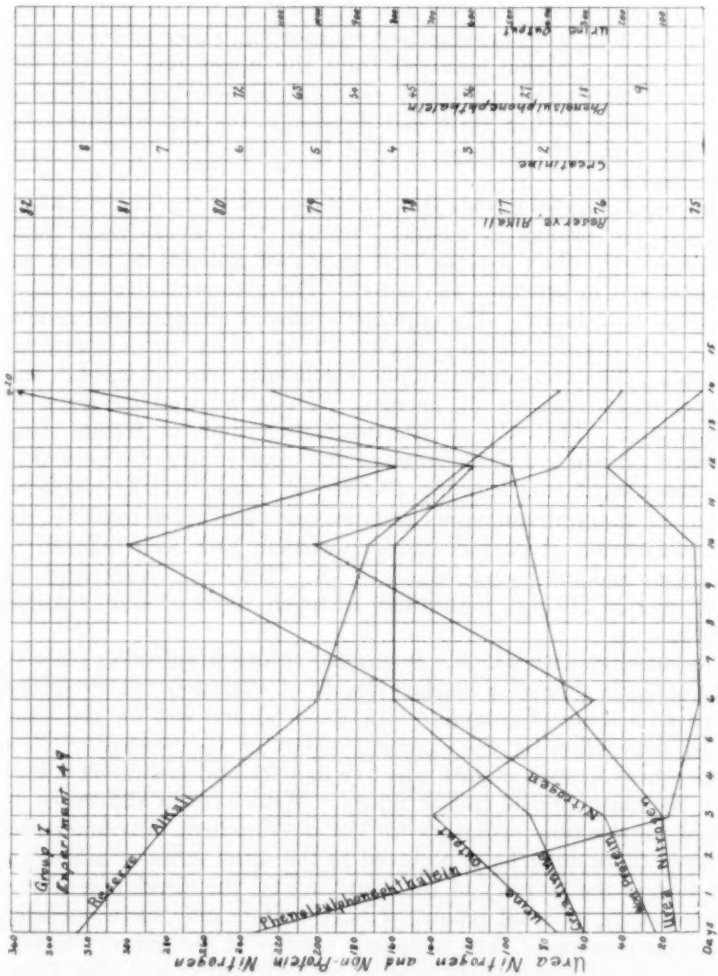


CHART II

with the processes of repair the functional value of these organs which finally resulted in their return to a state of normal renal function. From the commencement of the acute injury until such a normal response had been obtained the experiments were terminated at suitable periods to trace the transition from one of depressed function to one of normal function. In this group it furthermore

became necessary to know that in the kidney of a given animal there had existed a certain type of acute degenerative reaction associated with diminished renal function, and that in the kidney of this specific animal changes of repair had resulted in a return to normal function. For this purpose, in 8 of the animals before there was any functional evidence of recuperation after the kidney had been protected by a glucose solution[34] against the toxic action of the anesthetic, the dogs were anesthetized by morphin ether and a wedge-shaped piece of tissue removed from the upper pole of the left kidney. The animals recovered and finally returned to a functional normal. After such a state had developed the experiments were terminated and the kidneys studied in relation to the functional recuperation.

The renal changes in this group of dogs during the stage of acute nephritis are similar in location, though less severe than those previously described for the first group of animals in which no improvement in function was noted. The glomerular vessels were distended with blood. The capillary endothelium appeared prominent, with deeply staining nuclei. There were no subcapsular exudates. The convoluted tubule epithelium was edematous and showed early changes of necrosis. There was no evidence of regeneration. The cells of the descending limb of Henle's loop appeared normal. At this stage of the renal injury the animal of this experiment was forming 537 cc. of urine, which contained 0.5 gm. of albumin, numerous granular casts and a few hyalin casts. The elimination of phenolsulphonephthalein had been reduced to 5 per cent and the reserve alkali to 7.8. There was a retention of blood urea of 70 mg., nonprotein nitrogen 120 mg. and creatinin 4.75 mg.

The rapidity with which a functional recuperation takes place in these animals showed a marked degree of variation. The earliest return to a state of complete functional normal was on the nineteenth day following the commencement of the nephritis. The latest return to such a state was five months and twenty-two days from the date of the initial injury. With such a difference in animals in the time necessary for the development of a functional recovery there must have occurred in the same series of animals a variation in the severity of the acute injury, the development of a different type of renal repair, or both factors may have operated in the same animal. The histologic studies of the kidneys in animals which recovered show that in both the rapid and slow types of recovery the acute injury is characterized by but slight structural changes in the glomeruli. The degree of epithelial injury shows a variation and the dominant type of epithelial repair is entirely different in the animals which have varied so much in the length of time necessary to effect a return to normal function. In those animals in which a rapid resumption of renal function took place

the convoluted tubule cells were not lost. Following an injury associated with edema and moderately severe necrosis a regeneration of these cells took place from preëxisting cells. In animals in which there is a delayed period for functional recovery the epithelial replacement takes place to a minor degree by the process just described while the dominant type of repair is by an entirely different process. Many of the convoluted tubule cells which have become necrotic and have disappeared are replaced by these tubules becoming lined by a flattened, apparently less specialized cell with prominent and deeply staining nuclei. The tubular lining may have a syncytial-like appearance with imperfect cell differentiation.

On the twenty-fourth day of the nephritis in the animal under consideration there was an output of 400 cc. of urine which was free from albumin but which contained finely granular and hyalin casts. The elimination of phenolsulphonephthalein had increased from 5 to 45 per cent and the reserve alkali of the blood had increased from 7.8 to 8.1. The retention of blood urea was reduced from 70 to 15 mg., nonprotein nitrogen from 120 to 30 mg. and creatinin from 4.75 to 1.5 mg. With but slight variation from the normal, this type of response continued into the fifth month, when the animal became functionally normal. At the termination of the experiment the histologic study showed the glomeruli varying much in size and structure. Many of these units showed a connective-tissue obliteration of the loops, while other capillaries contained blood. The capsules showed a thickening which was variable and frequently the capillary tufts were in areas adherent to the capsule. The glomerular damage was not uniform.

The epithelium of the convoluted tubules showed two entirely different types of repair. The first type is characterized by the formation through regeneration from less severely injured convoluted tubule cells of an epithelial replacement very similar to cells normal for this part of the tubule. The second and more usual type of repair was by an entirely different type of flattened cell atypical for this location in the tubule.

The animals in this series were young dogs between one and two years of age which developed, as did the older animals, a severe acute nephritis from uranium. The fact that such a condition existed was not only established by a functional comparison of the two groups, but by the removal from the kidney in certain of the animals of the latter group before any evidence of functional recuperation had commenced of tissue which served as a histologic control for a specific animal of the group. The changes in such control tissue consisted in an acute epithelial degeneration of the cells of the proximal convoluted tubules and with but only slight evidence of structural injury to the glomeruli. Later in the course of nephritis the epithelial regeneration of two entirely different types developed in the injured tubules. The glomeruli at this time

showed evidence of a preëxisting injury by the formation of connective tissue with the obliteration of capillary loops and thickening of the capsules. Connective tissue was formed in the periglomerular and intertubular areas.

The functional response shown by these animals during the acute nephritis and during the changes of repair with the establishment of a state of normal renal function are as follows: The animals became polyuric with an albuminous urine containing casts. There was a rapid reduction in the elimination of phenolsulphonephthalein, a decrease in the reserve alkali of the blood, a retention of urea, nonprotein nitrogen and creatinin. This response is similar up to a certain stage with the response obtained from the first group of animals which failed to recuperate. In the second series of animals changes of repair developed which enabled the dogs finally to return to a functional normal. The time limit for this process varied, but the character of the reaction was the same. This return to the normal was associated in all of the animals with a regeneration of convoluted tubule epithelium of two types. The dominant cytologic type regenerated in the different animals varied. At the same time that such processes of repair occurred in the tubules there developed fibrous-tissue changes of an obliterative character in the glomeruli which were not uniform in severity or distribution. The functional expression of such types of repair have consisted in a decrease in urine formation to or toward the animal's normal daily output, a decrease and final absence of albumin from the urine and with a change in the character of the casts from a granular to a hyalin type. In a certain number of the animals the casts disappeared. Associated with these changes in the urine there was a gradual increase in the elimination of phenolsulphonephthalein, a decrease in the depletion of the reserve alkali to the normal and a decrease in retention of urea nitrogen, nonprotein nitrogen and creatinin until these values reached the normal. (Charts III and IV.)

A final series of young dogs which were given 4 mg. of uranium nitrate per kilogram, after developing an acute nephritis, failed to effect a functional restoration, but were left with such histologic changes in the kidneys and such evidence of renal dysfunction that they could be classed as animals with a chronic nephritis. In this group of 38 dogs functional studies were made in connection with the histologic studies of the kidneys from a period of two days following the commencement of the nephritis, through the period of repair and for five years and four months into the stage of functional stabilization which may be looked upon as the animals' pathologic normal or chronic nephritic state. Both the functional and anatomic changes during the stages of acute nephritis and of repair resembled those of the second group of animals with the exception that the animals in the former group were able to establish a complete restoration of function while this last group of animals were unable to effect such a return to the normal. Eight dogs of

this group showing quantitatively the same type of response as other members of the group in the acute stage of the injury were anesthetized by morphin ether and renal tissue removed from the upper pole of the left kidney to serve as a control for the acute stage of the injury and for the subsequent stages of repair. The study

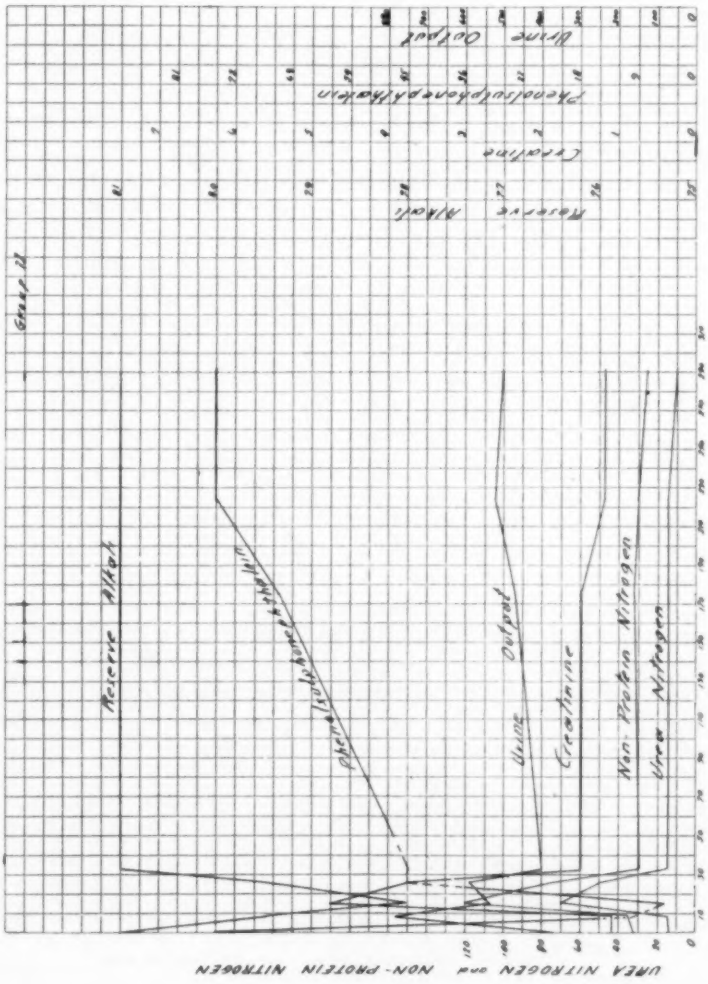


CHART III

of such tissues in connection with the functional response of the animals when it was obtained showed the same type of degenerative changes as has been described in such dogs in the previous groups. The terminal studies were made in animals in which a chronic nephritis had existed for as short a time as four months and in other dogs over as long a period as five years and two months.

The study of the following animal is characteristic for the members of the group. On the sixth day of the acute nephritis the dog was polyuric, with an output of 1200 cc. of urine, which contained 2 gm. of albumin per liter and numerous granular and hyalin casts. There was no elimination of phenolosulphonephthalein in a two-

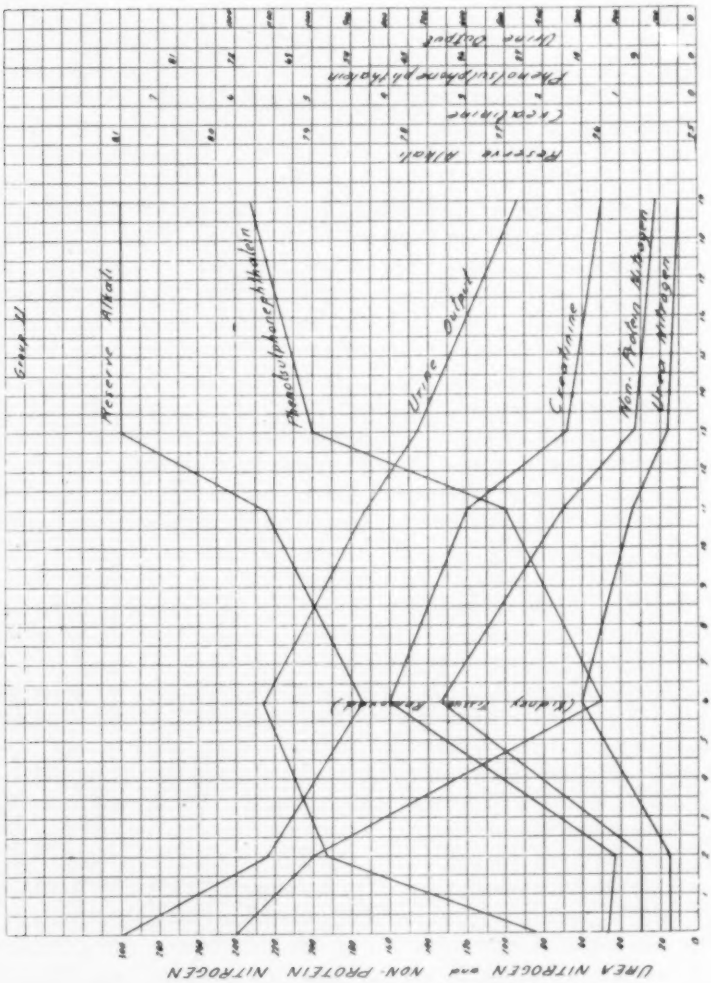


CHART IV

hour period, the reserve alkali was reduced from the normal of 8.1 to 7.8; there was a retention of 45 mg. of blood urea, 78 mg. of non-protein nitrogen and 4.6 mg. of creatinin. On the twenty-fifth day the amount of albumin had decreased but with little change in the number and character of the casts. There was a trace of phenolsulphonephthalein eliminated in a two-hour period and an increase

in the reserve alkali to 7.9. The evidence of retention had increased so that the blood showed 100 mg. of urea nitrogen, 128 mg. of nonprotein nitrogen and 6.1 mg. of creatinin. On the thirty-fifth day of the experiment there was an output of 511 cc. of urine which contained albumin, but a decrease in the number of granular casts and a relative increase in the hyalin type. The elimination of phenolsulphonephthalein was 12 per cent, the alkali reserve of the blood had increased to 7.95, the retention of urea had decreased to 33 mg., nonprotein nitrogen to 50 mg. and creatinin to 3.1 mg.

From this period to the termination of the experiment, two years and three months from its commencement, the functional response of the animal varied but little. At this time, with an intake of 500 cc. of water, the dog was forming 811 cc. of urine, which contained albumin and hyalin casts. There was an elimination of 34 per cent of phenolsulphonephthalein, a normal alkali reserve of the blood of 8.1, a retention of blood urea of 30 mg., of nonprotein nitrogen of 54 mg. and creatinin 2.4 mg.

The chronic renal changes which developed as a result of an attempt at repair which failed to reëstablish a state of normal renal function are as follows: The kidneys were small, with an irregular surface and the capsule thickened and adherent. On section, the kidney showed a decided thinning of the cortex. The histologic study showed a general glomerular fibrosis which varied in intensity in different glomeruli. All of these structures had participated in the reaction to some extent. Many of the capillary loops had been obliterated by connective-tissue formation. In some of the glomeruli this process was complete with a later hyalinization of the fibrous tissue. In other units this obliteration had been partial with the remaining loops with thickened walls containing blood. The glomerular capsules showed a connective-tissue thickening to which the fibrous capillaries were often adherent. Hyperplasia of the capsular epithelium was rarely observed. Many of the tubules had disappeared, with a replacement of masses of fibrous tissue. The smaller arteries with thickened middle coats were numerically prominent. The convoluted tubules which remained were lined by two types of cells. The first type, in which degenerative changes were still occurring, had in general the appearance of convoluted tubule epithelium. Such cells appeared normal or more usually they had a granular structure, stained imperfectly and in many instances the nuclei were hypochromatic or had disappeared. This type of cell is likely one of the regenerated types previously described, many of which have later undergone processes of degeneration.

The second and usual type of cell to be found in the convoluted tubules at such a stage of repair with the development of a chronic nephritis is a regenerated cell of an entirely different order. The epithelium is in the form of a cytoplasmic layer which may or may

not be differentiated into cells with definite cell boundaries. They line the tubules with a low flattened type of epithelium with large, deeply-staining nuclei. They do not have the specialization in histologic structure characteristic of proximal convoluted tubule epithelium. The cell is atypical for this part of the tubule. (Charts V and VI.)

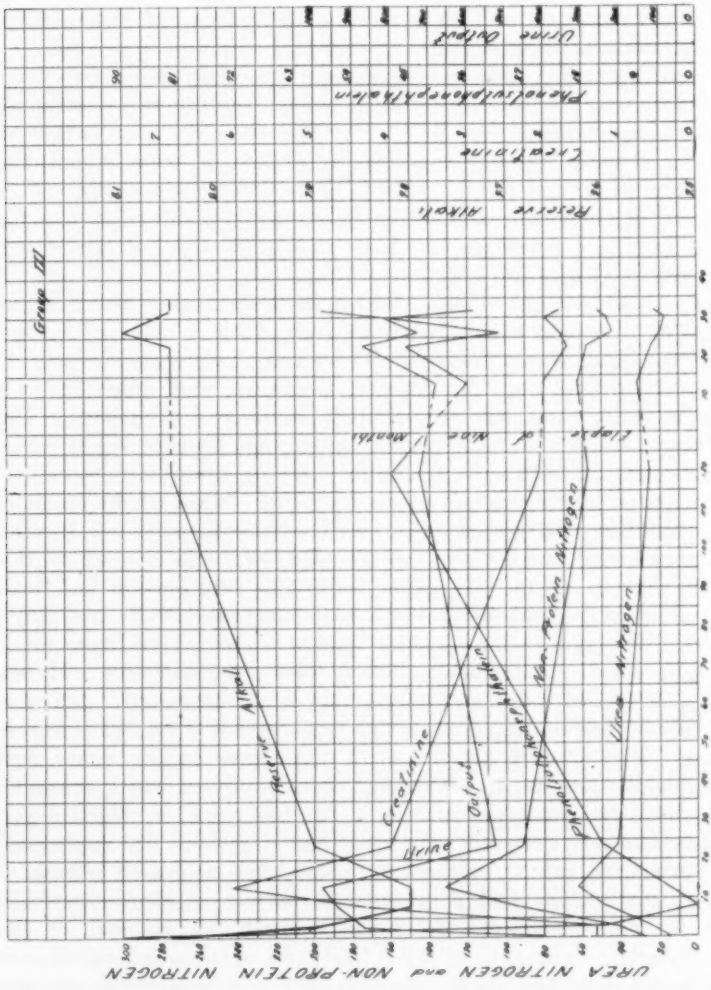


CHART V

In connection with the terminal pathology shown by these dogs as well as by the same animal and other animals of the group before the development of the terminal changes, it becomes desirable to review the sequence of the functional response shown by the dogs of the group. As early as the second day following the development

of an acute nephritis the animals became polyuric, with an albuminous urine containing granular casts. There was a marked reduction in the elimination of phenolsulphonephthalein, or it failed to appear in the urine in a two-hour period. The reserve alkali of the blood was reduced to as low as 7.8 and a retention occurred in blood urea,

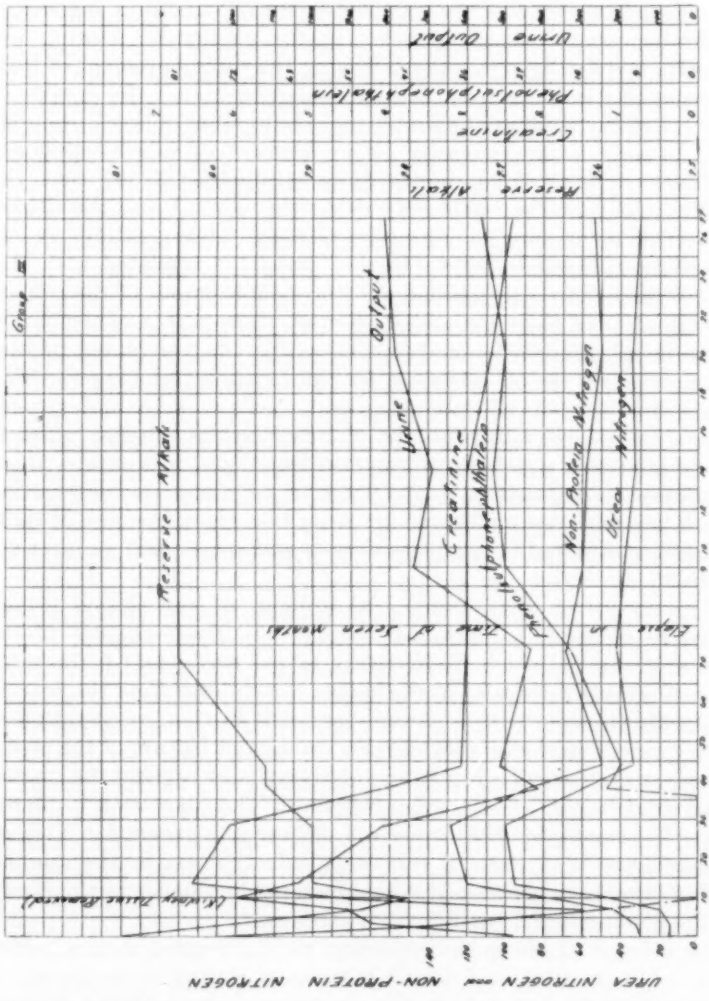


CHART VI

nonprotein nitrogen and creatinin. At such periods of renal functional depression there was slight evidence of structural glomerular injury and marked evidence of proximal convoluted tubule degeneration with early necrosis. The severity of these functional changes increased to a period in the respective experiments which varied between the sixth to the sixteenth days. At such periods

the amount of albumin and number of granular casts diminished, phenolsulphonephthalein reappeared in the urine or increased in its percentage elimination, the reserve alkali of the blood increased and the retention of urea, nonprotein nitrogen and creatinin diminished. Such functional expressions of improvement were anatomically associated with epithelial regeneration in the proximal convoluted tubules and the commencement of structural changes of a chronic degenerative character in the glomeruli. During the months, and finally the years, following the commencement of such changes the urine output usually remained above the intake of water, and the amount of albumin and the number of finely granular and hyalin casts decreased. The amount of phenolsulphonephthalein eliminated has increased to as much as 35 per cent, the reserve alkali of the blood returns to the normal and the degree of retention of urea, nonprotein nitrogen and creatinin, while diminishing, failed to return to the normal. Correlated with this improvement in renal function and the establishment of the respective animals of their pathologic normal, there was a continuation of epithelial regeneration and replacement in the convoluted tubules of an atypical type of epithelium for this location and a regeneration of a normal type of cell which frequently gives evidence of degeneration. Associated with this type of repair to the tubules, which is interpreted as a cytologic attempt at functional restoration, there developed a continuation in the processes of glomerular destruction which had not been uniform in intensity but which in many of these bodies had resulted in complete fibrosis and subsequent connective-tissue hyalinization.

This group of dogs, unlike the animals of the second group, failed to establish a functional normal. In those animals of the second group, in which the recovery period was delayed, the same type of process developed in the kidney but differed from the process in the third group with a chronic nephritis in that regeneration of both types of epithelium was a more prominent feature of the repair process and glomerular injury and obliterative changes in the smaller renal arteries was a less marked feature. The suggestion is offered that the reason for the imperfect epithelial regeneration and its maintenance in a state of functional effectiveness in the animals with a chronic nephritis is due to a final predominance of the injury to the glomeruli and smaller renal arteries.

As a result of these studies which have extended over a period of nearly six years, and which have been controlled in groups of animals and, furthermore, in the same animal by anatomic observation in relation to function disturbance, it becomes extremely difficult not to ascribe certainly to the proximal convoluted tubules a secretory function from without in, rather than to ascribe to them only the function of secretion or absorption from within out of substances formed at the glomerulus and found in their tubular urine.

It will be recalled from an earlier part of this discussion that a certain number of animals after they had recovered from the acute nephritis so extended the processes of renal repair as to make a complete functional recovery. This recovery was associated with early connective-tissue changes in the glomeruli and their capsules, in the periglomerular and intertubular spaces and were common for all of the animals which recovered. As these changes progressed, the type of convoluted tubule repair which predominated in the animals showed a marked difference. In certain animals of this series the convoluted tubules were repaired by the regeneration of an epithelium closely resembling that which is normal for such tubules. In other animals, although this same type of repair developed, the dominant type of regeneration and in areas the only type found was of a flattened, much less specialized cell with prominent nuclei. Suzuki[35] first made the observation that this type of cell was resistant to uranium. Somewhat later, and without knowledge of Suzuki's work, a similar observation was made in my laboratory, and, in addition, it was shown that such an epithelial lining of the convoluted tubules which were found in areas of repair in the kidney of dogs with a naturally acquired chronic nephritis were resistant to the general anesthetics as well as to uranium.[36] Gil and Gil[37] and Hunter,[38] in much later observations studied the histogenesis of such epithelial replacements and their resistance to uranium. In order to obtain more information concerning the resistance of renal epithelium to uranium and with the hope of strengthening the observations previously made concerning the functional value of convoluted tubule epithelium the following experiments were undertaken:

A group of 41 dogs (Group IV) were given an acute uranium nephritis by the subcutaneous injection of 2 mg. of uranium nitrate per kilogram and their functional response studied during the course of the acute renal injury and the period of repair. After these animals had returned to a functional normal a certain number were anesthetized by morphin ether and a wedge of renal tissue removed to check the then existing histologic changes with the functional return and to ascertain the type of epithelial repair which had been associated with the reëstablishment of renal function. Such material also served as a control for subsequent changes developing in the kidneys of a given animal. This tissue has shown in different animals the two types of epithelial repair which have been previously described—either a predominant type resembling normal convoluted tubule epithelium or the flattened type which is atypical for this portion of the tubule. After having established the type of tubular repair which predominated in the animals the animals were given a second subcutaneous injection of either 2 or 4 mg. of uranium nitrate per kilogram. The functional response of these two groups of animals with a similar type of glomerular injury, but with predominatingly dissimilar types of epithelial repair were

entirely different. Those animals which had effected an epithelial repair by the regeneration of renal epithelium closely resembling morphologically that of the normal proximal convoluted tubule reacted functionally in a manner similar to, though more intensely than they did from the initial injection of uranium. The urine contained as high as 7.2 gm. of albumin per liter. The elimination of phenolsulphonephthalein was rapidly reduced to a trace or fails to appear in the urine, the reserve alkali of the blood was brought to as low as 7.7 and there developed the usual marked retention of urea, nonprotein nitrogen and creatinin. A certain number of these animals failed to survive the second injection of uranium. They developed an air hunger with or without convulsions. The changes in the kidney were similar to or more severe than the acute injury obtained from the primary use of uranium. The glomerular changes were similar to those noted after the recuperation from the initial acute nephritis and, in addition, showed an acute engorgement of the patent capillaries with blood and rarely a subcapsular exudate. The changes of degeneration in the repaired or regenerated convoluted tubule cells consisted in edema, vacuolation and extensive necrosis. In cells which remained attached to the basement membrane evidence of an attempt at repair was noted in the occurrence of mitotic figures. The dogs of this series which recuperated from the first injection of uranium and as a part of the process of repair regenerated an epithelium, similar to convoluted tubule epithelium, show no resistance to a second intoxication by it.

In the second group of animals the establishment of a functional normal was associated with a similar type of chronic injury to the glomeruli, as has been described for the first group, and by the regeneration in the proximal convoluted tubules of two entirely different types of cells. The first type resembles cells which are usual for this portion of the tubule and which have been shown to have no resistance for uranium. The second type, which has been the predominant form of regeneration in this group of animals, is of the atypical, flattened type of cell. When a second subcutaneous injection of 2 or 4 mg. of uranium was given to an animal with this type of epithelial repair to the convoluted tubules the functional response of the animal was entirely different from that of those of the first group. In this latter group there is a transitory increase in the formation of urine which has not contained over 1.3 gm. of albumin per liter with a small number of granular and hyalin casts. The elimination of phenolsulphonephthalein was but slightly reduced and the reduction in the reserve alkali of the blood has either failed to occur or it was not reduced below 8. There was no appreciable increase in the retention of urea, nonprotein nitrogen and creatinin. Following such slight changes in renal function from the secondary injection of uranium, the animals returned to the state of renal functional response previously established from the

primary injection of uranium. The kidneys of such animals showed in the glomeruli an increase in the degree of fibrosis over that observed following the changes of repair secondary to the first acute nephritis from uranium. The convoluted tubules showed three types of changes. The majority of the tubules were lined by the

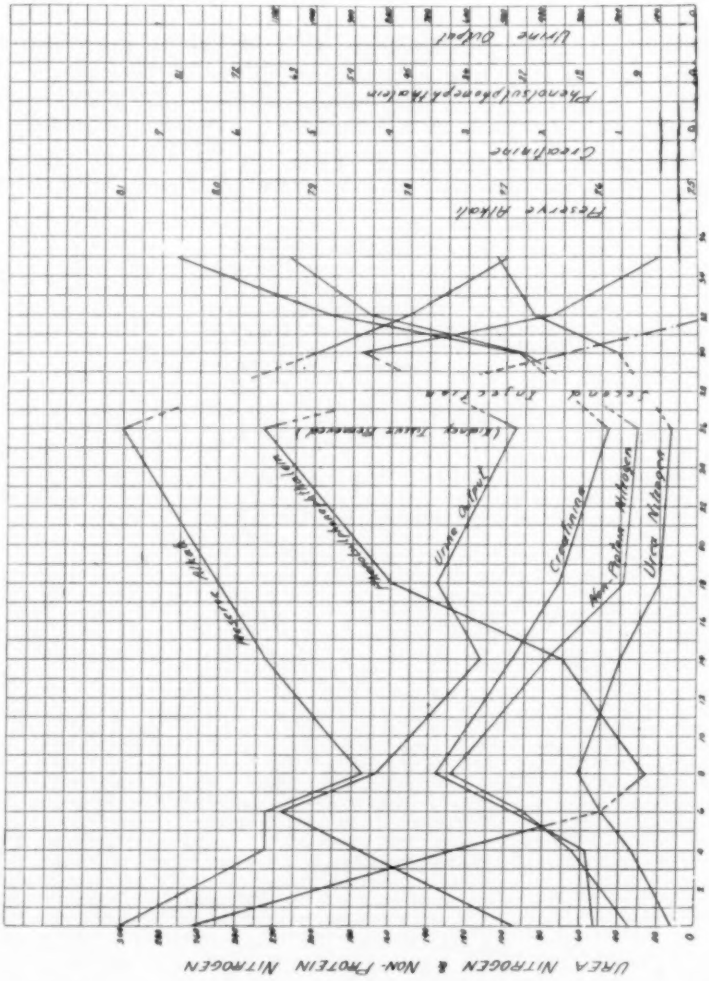


CHART VII

flattened, atypical type of epithelium, which gives to such kidneys their resistance to uranium. In such areas there was no evidence of degeneration from the second injection of uranium, which in certain of the dogs was given in twice the original amount. In other tubules there was both evidence of cell degeneration of epithelium normal for the convoluted tubules and repair by the flattened type of cell, and, last, there were tubules in which there

were no changes of repair but only evidence of epithelial degeneration. (Charts VII and VIII.)

These final experiments lend emphasis to the functional value as secretory units of the proximal convoluted tubules. They, furthermore, show the resistance of the kidney to a secondary nephrotoxic action from uranium to be dependent upon the ability of the kidney

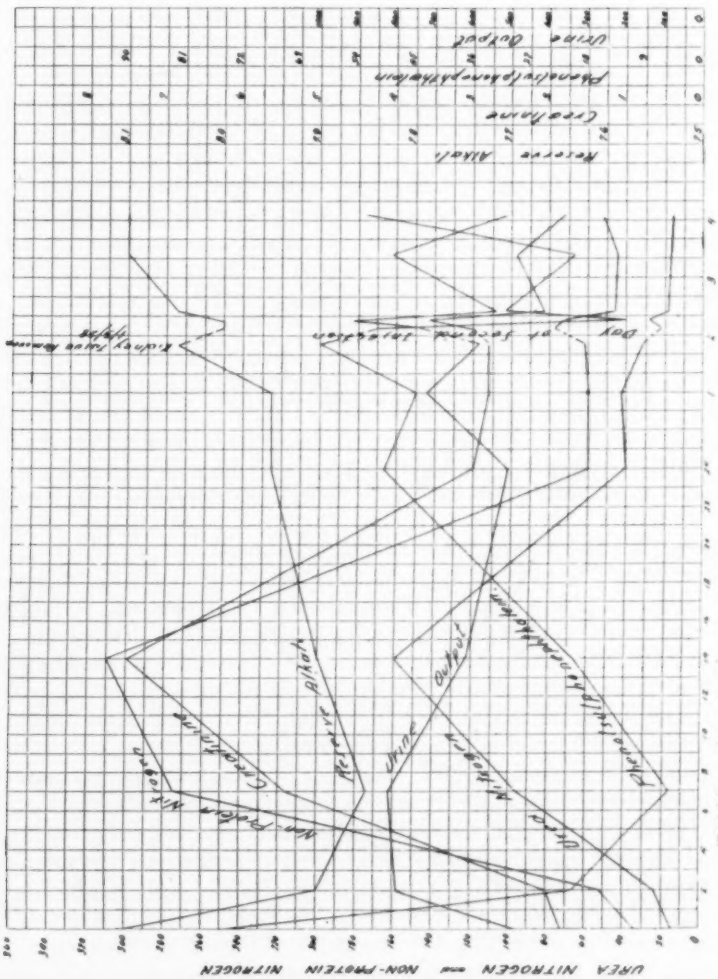


CHART VIII

to repair its epithelial injury by the formation of an atypical epithelium for the convoluted tubules and not by the regeneration of a specialized cell closely resembling those which are normally found in these tubules. The suggestion is made that this type of repair may in part constitute a defense mechanism for one element of renal structure against future injury.

The evidence presented in this lecture, which largely concerns itself with an analysis of the functional value in terms of secretion of the epithelium of the proximal convoluted tubules, is lacking in absolute proof, for these structures have not been separated from other interrelated structures, and as such their functional values determined. For the higher animals this probably cannot be completely accomplished. In such animals the exact function of a particulate but intimately related structure can only be ascertained by finally gaining an understanding of such structures in terms of their functional evolution. When this type of research is welded together in a functional whole renal function will be understood in the higher animals just as similar studies of structural evolution have given us an understanding of its highest complexity in man.

BIBLIOGRAPHY.

1. Marine, D.: Johns Hopkins Hosp. Bull., 1907, **18**, 359.
2. Dolley, D. H.: J. Med. Res., 1909, **20**, 275.
3. Banting, F. G., Best, C. H., and Macleod, J. J. R.: Am. J. Phys., 1922, **59**, 479.
4. Aschoff, L.: The Harvey Lectures, 1923–1924.
5. Leconte, C.: Gaz. méd. de Paris, 1854, **9**, 488.
6. Richter, P. F.: Berl. klin. Wchnschr., 1905, **42**, 384.
7. Chittenden, R. H., and Hutchinson, M. T.: Trans. Conn. Acad. Arts and Sci., 1886, **7**, 261.
8. Chittenden, R. H., and Lambeth, A.: Trans. Conn. Acad. Arts and Sci., 1888, **8**, 1.
9. Wallace, G. B., and Myers, H. B.: J. Pharm. and Exp. Therap., 1913–1914, **5**, 511.
10. Schirokauer, H.: Ztschr. f. klin. Med., 1908, **66**, 169.
11. Heineke, A., and Myerstein, W.: Deutsch. Arch. f. klin. Med., 1907, **90**, 101.
12. Christian, H. A.: Boston Med. and Surg. J., 1908, **159**, 8.
13. Christian, H. A., Smith, R. M., and Walker, T. C.: Arch. Int. Med., 1911, **3**, 468.
14. Christian, H. A., and O'Hare, J. P.: J. Med. Res., 1913, **28**, 227.
15. Pearce, R. M.: Arch. Int. Med., 1910, **5**, 133.
16. MacNider, W. deB.: J. Med. Res., 1912, **26**, 79.
17. MacNider, W. deB.: J. Pharm. and Exp. Therap., 1912, **3**, 423.
18. MacNider, W. deB.: J. Pharm. and Exp. Therap., 1913, **4**, 491.
19. MacNider, W. deB.: J. Pharm. and Exp. Therap., 1914, **6**, 123.
20. MacNider, W. deB.: J. Exp. Med., 1917, **26**, 1.
21. MacNider, W. deB.: J. Exp. Med., 1917, **26**, 19.
22. MacNider, W. deB.: J. Exp. Med., 1918, **28**, 517.
23. MacNider, W. deB.: J. Exp. Med., 1916, **23**, 171.
24. MacNider, W. deB.: J. Pharm. and Exp. Therap., 1926, **29**, 381.
25. Goto, K.: J. Exp. Med., 1917, **25**, 693.
26. Suzuki, T.: Morphologie der Nierensekretion, Jena, 1912.
27. Mitamura, T.: Arch. f. gls. Physiol., Berlin, 1924, **204**, 561.
28. Marriott, W. McK.: Arch. Int. Med., 1916, **17**, 840.
29. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem., 1917, **30**, 347.
30. Rowntree, L. G., and Geraghty, J. T.: J. Pharm. and Exp. Therap., 1909–1910, **1**, 579.
31. Marshall, E. K., Jr.: J. Biol. Chem., 1913, **14**, 283.
32. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem., 1914, **19**, 211.
33. Folin, O., and Wu, H.: J. Biol. Chem., 1919, **38**, 81.
34. MacNider, W. deB.: J. Pharm. and Exp. Therap., 1926, **29**, 381.
35. Suzuki, T.: Morphologie der Nierensekretion, Jena, 1912.
36. MacNider, W. deB.: J. Med. Res., 1916, **34**, 177.
37. Gil y Gil, C.: Beiträge zur path. Anat., 1924, **72**, 621.
38. Hunter, W. C.: Ann. Int. Med., 1928, **1**, 747.

WATERMELON-SEED EXTRACT IN THE TREATMENT OF HYPERTENSION.

By. T. L. Althausen, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA,
AND
Wm. J. Kerr, M.D.,
PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA.

(From the Department of Medicine, University of California Medical School, San Francisco.)

In 1926, Barksdale[1] investigating extracts of the seed of the watermelon (Cucurbita citrullus) isolated a physiologically active glucoside-saponin which he named "cucurbocitrin." The main effect of cucurbocitrin in normal dogs and man is that of lowering the arterial tension. Direct microscopic measurements on capillaries of the frog showed that their diameter was more than doubled after administration of the drug. Similarly studies with the Danzer-Hooker microcapillary tonometer in man revealed a lowering of the capillary pressure from an average of 16 mm. before to an average of 9 mm. after the administration of this substance, thus strongly suggesting that reduction in the blood pressure is brought about by capillary dilatation. The possibility that the action of cucurbocitrin is due to cardiac depression was ruled out by direct perfusion experiments with the frog's heart.

Cucurbocitrin is active when given by mouth and its use is perfectly safe. Twenty milligrams of it produces definite lowering of the blood pressure in normal individuals, and as much as 300 mg. have been given in a single dose without ill effects. The lethal dose for rabbits is 200 mg. per kilo of body weight. For details of the chemistry and pharmacology of cucurbocitrin the reader is referred to the original article of Barksdale.[1]

Clinically, cucurbocitrin was tried by Barksdale with success in 10 cases of hypertension due to tuberculous nephritis, but his results with high blood pressure in several arteriosclerotic patients were unsatisfactory. Wilkinson[2] reported the use of this drug in 68 cases of "hypertensive cardiovascular disease" obtained in coöperation with some twenty physicians. In this series 56 out of the 68 patients "showed a sufficient reduction in the arterial tension to be of clinical importance and the relief of symptoms was frequently out of proportion to the drop in pressure." The author feels that cucurbocitrin is more efficacious in hypertension associated with the menopause, senility and obesity.

With this information at hand it seemed worth while to subject to cucurbocitrin therapy a thoroughly studied and well-controlled

group of clinical patients with hypertension, in an attempt to determine, if possible, the type or types of hypertension responding favorably to this treatment. Our second aim in undertaking this work was a comparison of the results obtained by cucurbocitrin with those achieved with liver-extract therapy.

The present study was made possible through the courtesy of Dr. I. S. Barksdale and the Table Rock Laboratories of Greenville, South Carolina, by whom the drug was supplied.

Selection and Examination of Patients. We realized the obstacles encountered in any experiment involving deductions from a therapeutic procedure and the particular difficulties involved in dealing with hypertension. For this reason, the work was carried out as much as possible in the out-patient department where the patients' habits and environment could be left undisturbed, thus eliminating the most important factor of uncertainty which enters into the appraisal of results obtained in the treatment of hypertension in hospitalized individuals. In all but four cases, the treatment was carried out entirely in the Clinic. Moreover, two of the three hospital cases in which reduction of blood pressure was produced were followed later in the out-patient department. In the hospitalized patients, cucurbocitrin therapy was started only after the blood pressure had become stabilized in the new environment, the patients spending from seven to thirty-three days in bed before the beginning of treatment.

No selection of cases for cucurbocitrin medication was attempted, but a number of patients whose hypertension had failed to yield to liver-extract therapy were put on cucurbocitrin.

In every case, a complete history was taken and a general physical examination done with special attention to features indicative of involvement of the kidneys, heart and bloodvessels. The laboratory investigation included a complete analysis of urine, the phenolsulphonephthalein test, the Mosenthal test, and the blood Wassermann test. All reported cases had a negative Wassermann reaction. In addition, blood-urea and nonprotein-nitrogen determinations were done in 23 cases, but later discontinued when a preliminary analysis disclosed that they had no bearing on the success or failure of cucurbocitrin therapy. Teleroentgenograms of the heart and electrocardiograms were taken, as indicated.

The majority of patients before receiving cucurbocitrin had gone through a period of treatment by dietetic measures (especially withdrawal of salt), and sedatives (mostly luminal) without much success. It goes without saying that no other treatment having any possible influence on blood pressure was given to the reported cases during the period of cucurbocitrin administration.

Methods of Observation and Treatment with Cucurbocitrin. Blood-pressure measurements were carried out in the morning with the same sphygmomanometer applied to the right arm of patients

who had rested in the prone position for ten to fifteen minutes. The auscultatory method was used.

In determining the average blood pressure before treatment, at least several measurements were taken on different days and in the majority of cases the patients had been under observation for several months and often years prior to receiving cucurbocitrin. The average blood pressure following treatment was recorded for the entire period if the latter was less than one month and for the last month if it extended over several months, even if intermediate months showed a lower average.

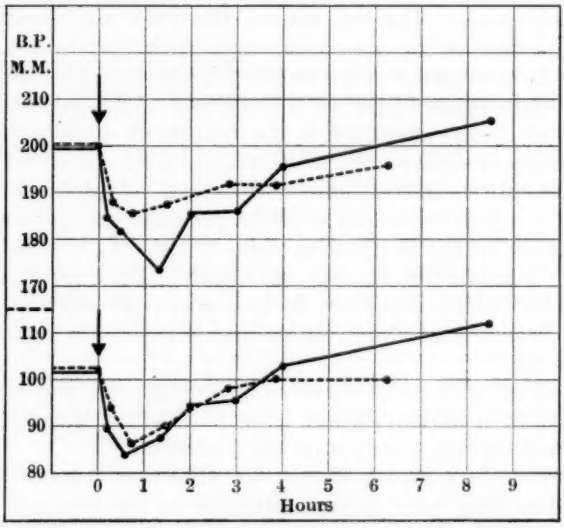


CHART I.—Chart showing immediate effects of cucurbocitrin on the systolic and diastolic blood pressure. The broken line indicates the effects of 100 mg. and the unbroken line those of 150 mg. of cucurbocitrin. Arrows indicate when cucurbocitrin was given by mouth.

In the case of patients who had received liver extract before cucurbocitrin, the latter was credited with reduction of hypertension only in comparison with the average blood-pressure level while receiving liver-extract injections unless at least three months had elapsed since the last injection, a period which, as experience has shown, is sufficient to exhaust the effect of liver extract in a great majority of even the most favorable cases.

Cucurbocitrin was given by mouth in capsules containing 50 mg. of the glucoside. After some preliminary experimentation an optimum dosage of one capsule three times a day was arrived at and used in most cases. To several patients 100 mg. and to one patient 150 mg. of the drug was prescribed three times a day. After two weeks of treatment it usually became apparent whether continuation of medication was indicated.

Results of Cucurbocitrin Therapy. I. *Immediate Effects:* Following a single oral dose of cucurbocitrin there is usually in hypertension cases a fall of the systolic and diastolic pressure beginning about fifteen minutes after the administration of the drug. The degree of reduction of blood pressure is more or less in proportion to the dose in the same patient, as can be seen from Charts I and II. The same is true in regard to the duration of the lowering of arterial tension following a single dose. It is of interest that patients often spontaneously reported diminution of symptoms even after one dose of the drug.

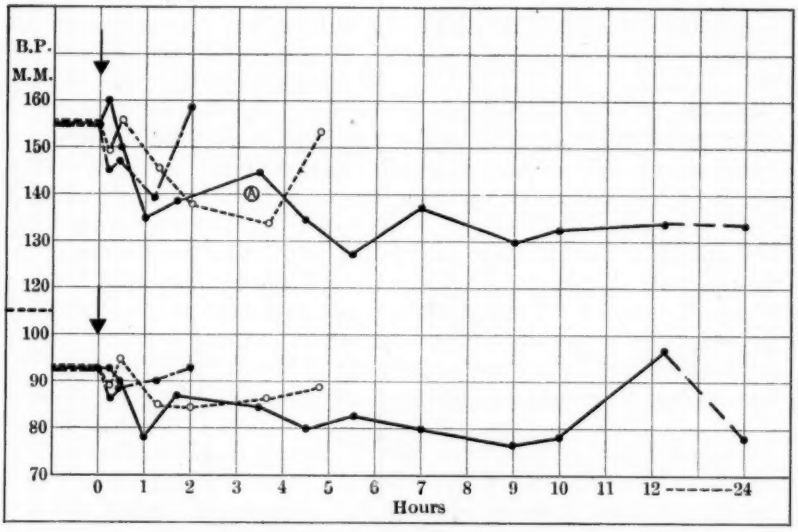


CHART II.—Chart showing immediate effects of cucurbocitrin on the systolic and diastolic blood pressure of another patient. The irregularly broken line shows blood pressure curves after 50 mg., the regularly broken line after 100 mg., and the unbroken line after 150 mg. of cucurbocitrin orally. Arrows indicate when cucurbocitrin was given. A, patient had lunch.

II. *Results of Prolonged Cucurbocitrin Administration.* In favorable cases, prolonged administration of cucurbocitrin brings about lasting reduction of hypertension which almost invariably is accompanied by symptomatic improvement of the patient. In Chart III are given blood-pressure curves from two cases of hypertension in which the latter was markedly reduced in the course of cucurbocitrin therapy. Altogether 40 cases of hypertension were given cucurbocitrin and the important clinical findings in each case summarized in Table I. Twenty-one of the 40 patients received injections of liver extract, 14 before and 7 after a period of cucurbocitrin administration and a comparison of the action of these two therapeutic remedies will be made at the end of this report. The average time of treat-

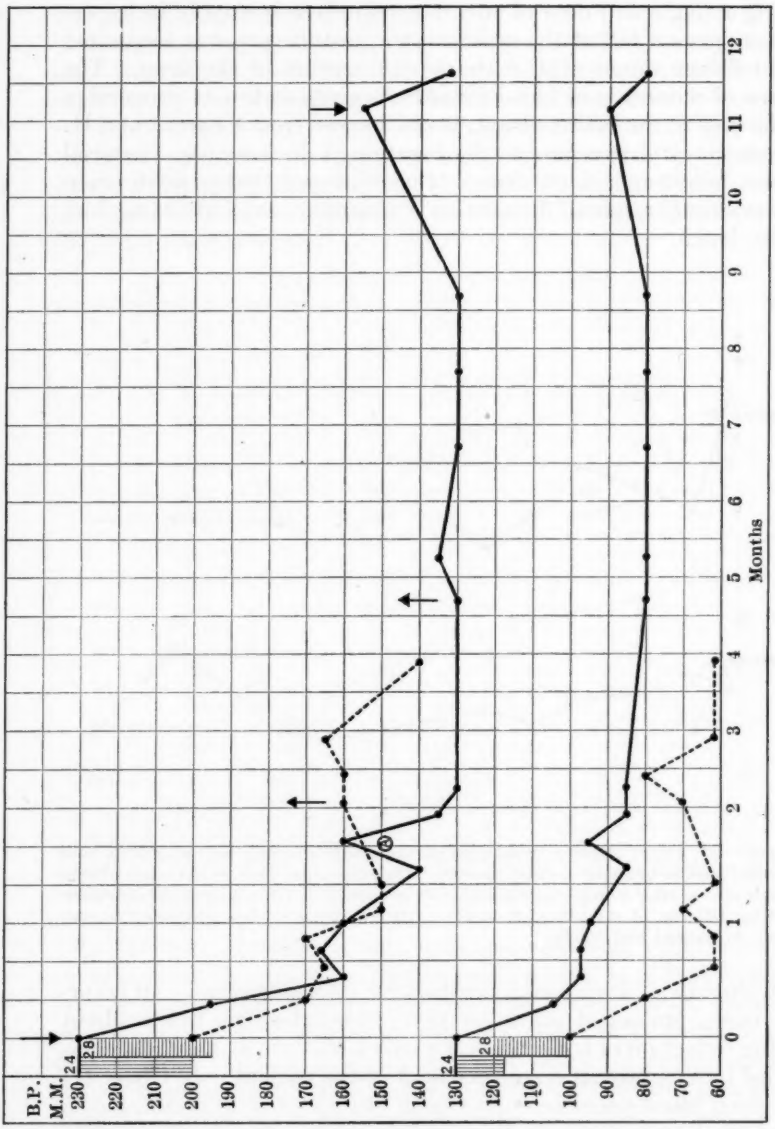


CHART III.—Chart showing prolonged lowering of the systolic and diastolic blood pressure in 2 hypertension cases (Nos. 24 and 28) who reacted favorably to cucurbocitrin therapy. Rectangles indicate the range of fluctuations of the blood pressure prior to curcurbocitrin administration. Arrows pointing down indicate the beginning of treatment. Arrows pointing up show discontinuation of cucurbocitrin. A, patient had respiratory infection with exacerbation of chronic choleecystitis.

ment with cucurbocitrin for 35 cases who responded by reduction of hypertension or improvement of symptoms, or both, was one hundred days. The average duration of cucurbocitrin therapy in 5 patients who failed to respond to treatment was thirty-eight days.

Lowering of the Average Systolic Blood Pressure. Lowering by 10 mm. or more took place in 29 out of 40 cases, or in 73 per cent of

all cases. The average lowering of systolic pressure in all cases who responded in this way was 22 mm. Since the majority of patients who received liver extract first were taken off liver-extract injections and put on cucurbocitrin because they did not respond satisfactorily to the former method of treatment, a certain adverse selection of intractable cases crept in. It is, therefore, of interest that the average reduction of the systolic blood pressure of the unselected group in which patients received cucurbocitrin first was 29 mm. Reduction of the diastolic pressure was usually in proportion to that of the systolic and the average for all cases amounted to 15 mm.

The greatest total fall in blood pressure in any one case was 81/43 mm. (from 211/123 to 130/80). The most marked reduction of blood pressure produced in a short period of time was 35/25 mm. in the first and in addition 35/7 mm. in the second week of cucurbocitrin administration in Case 26.

Symptomatic Relief. This was reported in 32 out of 39 cases with symptoms referable to hypertension or in 82 per cent of all cases. Of these cases 3 (or 9 per eent) reported complete relief of their symptoms; 18 (or 56 per cent) were markedly improved; and 11 (or 34 per cent) were partially relieved.

The symptoms given by patients in order of their incidence and those that were completely or markedly improved are given in Table II. The most frequent symptoms were: headaches, dyspnea, dizziness, palpitation, edema, tinnitus and visual disturbances. The complaints relieved in the largest per cent of their occurrence were: precordial pain, insomnia, dyspnea, palpitation, nervousness and headaches.

Partially relieved symptoms were omitted from this Table owing to a desire to exclude any possible psychic effects of the treatment.

Discussion. A reduction in blood pressure of 10 mm. or more was accompanied by symptomatic improvement in all but three cases and every patient whose blood pressure was reduced by 40 mm. or more was completely or markedly relieved of symptoms. On the other hand, even marked subjective improvement was at times reported without a corresponding lowering of hypertension.

Therefore, as in our preceding paper on the use of liver extract in the treatment of hypertension, it was found expedient to analyze separately the possible factors making for reduction in blood pressure and for symptomatic relief. In this manner, our successes and failures in these two respects are analyzed below from the standpoint of age, sex, degree and duration of hypertension, body weight, renal damage, cardiovascular changes, and the menopause in the female. A minimum reduction in the systolic pressure of 10 mm. and partial relief of symptoms were adopted as criteria of success in the following analysis, but the grouping of clinical data on the basis of a minimum reduction of 20 mm. and complete or marked symptomatic improvement was essentially similar.

TABLE I.—CLINICAL DATA AND EFFECTS OF CUCURBOCITRIN

Case.	Age.	Sex.	Duration of hypertension.	Deviation from normal weight in per cent.	Menstrual status.	Symptoms.	Physical findings.		Blood Pressure.			
							Cardiac signs.	Arterio-sclerosis.	Average before treatment.	Average after liver extract.	Average after cucurbocitrin.	Average reduction with cucurbocitrin.
1	48	F	1 yr.	13−	Hysterectomy 5 yrs. ago	Headache, nervousness, fatigue, dizziness; palpitation	Slight cardiac enlargement	Mod.	220 115	199 103	182 92	17 11
2	62	F	5 yrs.	2+	Menopause 12 yrs. ago	Headaches, dyspnea	Slight ankle edema; systolic murmur at apex	Mod.	196 91	199 89	180 96	19 7
3	49	M	2 yrs.	1+	....	Apoplexy 1 and 2 yrs. ago; fatigue	Systolic murmur at apex	Mod.	173 104	177 102	160 90	17 12
4	50	F	15 yrs.	14−	Menopausal symp. for one year	Headaches, dyspnea, palpitation, transitory blindness; hot flushes	Systolic murmur at apex. Ecg. S2 slightly slurred	Mod.	194 110	191 113	190 121	.. ..
5	59	F	3 yrs.	6−	Menopause 14 yrs. ago	Headaches, dizziness, fatigue, nervousness, visual disturbances, speech difficulties, lapses of memory, numbness of extremities, right facial weakness	Slight cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Mod.	258 136	255 123	250 130	 ..
6	49	F	4 mos.	25+	Menopause 4 yrs. ago. Rare hot flushes	Severe daily headaches	Systolic murmur at base	Mod.	229 140	203 115	215 145	14 5
7	50	F	3 yrs.	13−	CTA regular	Constant headaches, nervousness, lapses of memory, tinnitus, difficulties in walking, inability to dress	Systolic murmur at apex	Marked	190 106	193 102	175 98	18 4
8	41	F	3 yrs.	10+	CTA regular	Severe headaches, nervousness, tinnitus, palpitation, dizziness, sleeplessness.	Moderate cardiac enlargement	None	218 130	188 114	201 119	17 11
9	66	M	3 yrs.	3+	....	Dyspnea, headaches, dizziness, paralysis of right leg	Systolic murmur at base	Marked	217 107	219 100	210 70	 ..
10	28	F	2 yrs.	10−	CTA regular	None	None	None	185 105	197 118	190 120	 ..
11	53	F	4 yrs.	5+	Menopause 8 yrs. ago	Headache, palpitation, dizziness, dyspnea, precordial pain after heavy meals	Slight cardiac enlargement, systolic murmur at base, Ecg. right B. B. block; Roentgen ray aortic heart	Mod.	227 124	230 131	215 115	15 16
12	45	M	4 yrs.	21−	....	Headaches, dyspnea, epistaxis, right facial paralysis	Marked enlargement; loud A2; Roentgen ray aortic heart; Ecg. right B. B. block	Mod.	217 142	225 151	202 158	23 7
13	38	F	5 yrs.	9+	CTA regular	Headaches, dyspnea, precordial pain, palpitation, dizziness, blurring of vision	Slight enlargement; loud A2; systolic murmur at apex. Roentgen ray slight enlargement and hypertrophy	Mod.	250 139	215 106	207 105	43 34
14	54	M	7 yrs.	2+	....	Severe dizziness, epistaxis, slurring of speech, confusion, weakness, "stroke" affecting legs 1 yr. ago	Enlargement to left, loud A2; sounds of poor quality. Ankle edema; Ecg. partial A-V block; left preponderance	Marked	210 118	192 110	174 96	18 14
										After cucurbocitrin	After liver extract	
15	69	M	3 yrs.	2+	....	Severe daily headaches, dyspnea, fatigue, blurring of vision	Cardiac enlargement; Roentgen ray aortic heart; systolic murmur at base	Marked	263 144	255 137	238 123	 ..
16	51	M	6 mos.	20−	....	Headaches, dizziness, blurring of vision	Moderate cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Marked	193 127	178 110	174 111	15 17
17	48	M	1 yr.	20+	....	Headaches, dyspnea, palpitation, left hemiplegia	Slight ankle edema	Mod.	177 112	164 105	169 112	13 7
18	56	F	11 mos.	17−	Menopause 5 yrs. ago	Headaches, palpitation, fatigue, mental depression	Marked enlargement; loud A2, systolic murmur at apex; Roentgen ray hypertrophy and enlargement to left. Ankle edema	Mod.	235 140	228 134	227 135	 ..
19	46	F	2 yrs.	8+	CTA regular	Severe headaches, tinnitus, fatigue	Systolic murmur at apex	Mod.	197 95	198 75	194 74	..
20	43	F	6 yrs.	5+	CTA regular	Headaches, dyspnea, palpitation, nervousness	Slight enlargement; loud A2; systolic murmur at apex. Slight ankle edema; Roentgen ray slight enlargement	Mod.	249 133	233 113	230 124	16 20

IN A GROUP OF 40 HYPERTENSION CASES.

Laboratory findings.						Symptomatic relief from eucurbocitrin.	Symptomatic relief from liver extract.	Duration of eucurbocitrin therapy, days.	Previous treatment.	Remarks.
Urine.		Mosenthal test.		Phthalein test.	Blood chemistry mg. per 100 cc.					
Albumin.	Casts.	Nocturnal polyuria.	Fixation of specific gravity.							
0	0	0	0	80	Urea N. 20.1	Comp.	Comp.	90	None	
0	0	0	0	51	Urea N. 16.8	Marked	Mod.	250	Low salt, pyramidon	With double dose B. P. 170/97; 2 mos. without drug B. P. 190/80; 3 mos. without drug B. P. 220/80. Headache.
0	0	0	0	30	Urea N. 13.1	Marked	Marked	293	Low salt, low protein Luminal, Ki	3 weeks without drug, B. P. 182/100.
FPT	0	0	7 pts.	70	Urea N. 16.8	None	None	32	Low salt, low protein and fluids, luminal	
T.	Rare hyaline	0	5 pts.	32.5	Urea N. 21 N.P.N. 35.3	Mod.	None	43	Low salt, luminal, rest, Ki, ovarian extract	Roentgen-ray aortitis.
S. T.	0	+	6 pts.	55	N.P.N. 50	Marked	Marked	94	Low salt	1 mo. without drug no relapse.
F. P.T.	0	0	0	30	....	Marked	Marked	173	None	1 mo. without drug B. P. 185/105.
F. P. T.	0	+	4 pts.	50	....	Marked	Mod.	125	Low salt, low caloric, luminal	1 mo. without drug, headaches.
0	0	0	0	40	....	None	None	34	Low salt, luminal, allonal, Ki	
0	0	0	0	100	....	.....	.....	72	Low salt	
S.T.	0	0	0	55	....	Marked	Marked	157	Luminal	2 mos. without drug B. P. 250/130. Roentgen ray sclerosis of arch.
H.T.	Gran. cell and hyaline	+	0	30	Urea N. 25.2 N.P.N. 36.6	Marked	None	127	Low salt, low protein. Luminal	Rest in bed 8 days before treatment. With double and triple dose no greater effect; 1 mo. without drug B. P. 245/160. Roentgen ray enlarged and sclerotic arch.
0	0	0	7 pts.	70	....	Marked	Marked	180	None	Drug stopped twice for 6 weeks; symptoms recurred both times, B. P. 218/112 second time. Roentgen ray sclerosis of arch.
F. P. T.	Many hyalin	0	5 pts.	25	Urea N. 14.9 N.P.N. 28.5	None	None	54	Low salt, low protein bed rest. Catharsis	1 week without drug B. P. 190/110. Roentgen ray marked sclerosis of arch.
F. P.T.	Occ. hyalin and cell	+	0	32.5	Urea N. 17.3	Marked	Marked	87	Low salt, low protein, allonal, pyramidon q. 4 hrs.	Roentgen ray aortitis.
H. T.	Many hyalin	0	0	75	Urea N. 14	Mod.	Marked	14	Low salt, limited fluids, luminal, Ki	Roentgen ray sclerosis of arch.
F P.T.	0	0	0	55	....	Marked	Marked	72	Luminal	1 week without drug, B. P. 175/120. Headaches.
H.T.	0	+	0	55	Urea N. 14.2 N.P.N. 38.4	None	None	28	Low salt, low protein. Rest, luminal nitrites	Roentgen ray sclerosis of arch.
F.P.T.	0	0	3 pts.	60	....	Mod.	None	74	None	
F.T.	0	+	0	70	N.P.N. 44.4	Mod.	Mod.	51	Low salt, low protein, luminal, Ki	2 weeks without drug B. P. 260/130.

TABLE I.—CLINICAL DATA AND EFFECTS OF CUCURBOCITRIN

Case.	Age.	Sex.	Duration of hypertension.	Deviation from normal weight in per cent.	Menstrual status.	Symptoms.	Physical findings.		Blood Pressure.			
							Cardiac signs.	Arterio-sclerosis.	Average before treatment.	Average after liver extract.	Average after cucurbocitrin.	Average reduction with cucurbocitrin.
21	57	M	6 wks.	6+	....	Headaches, palpitation on exertion, epistaxis, parathesias of extremities, lapses of memory	Slight enlargement; sounds indistinct	Marked	176 106	163 108	173 103	13 2
22	57	F	6½ yrs.	8−	Menopause 4 yrs. ago	Headaches, palpitation, dyspnea	Slight cardiac enlargement; loud A2; systolic murmur at apex	Mod.	197 108	153 92	... ...	44 16
23	63	M	7 mos.	15−	....	Dizziness, unsteady gait	Slight cardiac enlargement; loud A2; diastolic murmur at base	Marked	240 130	217 117	... ...	23 13
24	50	F	8 yrs.	2−	Menopausal symptoms, hot flushes	Headaches, dizziness, insomnia	Loud A2, ankle edema	Mod.	205 103	160 70	...	45 33
25	63	F	5 yrs.	12+	Menopause 20 yrs. ago	Dyspnea; occasional cardiac pain, pain in eyes	Slight enlargement, systolic murmur at apex, ankle edema	Mod.	160 85	153 75	...	...
26	56	F	2½ mos.	13−	Menopause, 8 yrs. ago	Headaches, dyspnea	None	None	211 123	130 80	...	81 43
27	41	M	5 yrs.	7−	....	Headaches, dyspnea, palpitation, dizziness, insomnia, tinnitus, parasthesias of extremities	None	None	171 90	137 79	...	34 11
28	77	M	2 mos.	2−	....	Nervousness, fullness in head	Slight enlargement; loud A2	Mod.	196 105	153 67	...	43 38
29	38	F	1 mo.	25−	CTA regular	Severe headaches, dizziness, tinnitus	None	None	179 110	148 90	..	31 20
30	55	F	2 yrs.	15+	Menopause, 10 yrs. ago	Palpitation, dyspnea, tinnitus, nervousness	Enlargement to left, extrasystole; loud A2. Systolic murmur at apex. Ecg. shows left preponderance	Mod.	190 77	160 56	..	30 21
31	57	M	6 yrs.	7+	....	Precordial pain, dizziness, dyspnea, headaches	Marked enlargement, loud A2, systolic murmur at apex; Ecg. neg.	Mod.	217 112	195 77	...	22 35
32	42	F	8 yrs.	4−	Menopausal symptoms; irregular flow and hot flushes	Headaches, dyspnea, tinnitus	Moderate enlargement to the left. Systolic murmur at apex; Ecg. shows myocardial damage, slight ankle edema	Marked	220 128	192 123	...	28 5
33	62	F	15 yrs.	12−	Menopause, 17 yrs. ago	Dizziness, visual disturbances, tinnitus, impairment of memory, nervousness, speech difficulties, numbness of extremities, weakness	Slight enlargement, loud A2, systolic murmur at apex, Ecg. normal	Mod.	188 102	188 101	...	..
34	53	F	7 yrs.	1+	Menopause 7 yrs. ago	Headaches, dyspnea, visual disturbances	Slight enlargement, loud A2, systolic murmur at apex	Mod.	188 95	177 66	...	11 31
35	65	F	20 yrs.	1+	Menopause 2 yrs. ago	Headaches, dyspnea, palpitation, tinnitus, tachycardia, dizziness	Slight enlargement, systolic murmur at apex; Ecg. shows myocardial damage	Mod.	203 97	162 82	...	41 15
36	38	F	3 yrs.	8−	Menopausal symptoms	Headaches, dyspnea	Loud A2, systolic murmur at apex, ankle edema	None	231 129	221 140	... ...	10 11
37	56	F	2 yrs.	30+	Menopause 18 yrs. ago	Headaches, dyspnea, dizziness, continuous precordial pain	Moderate enlargement, loud A2, systolic murmur at apex, extrasystoles, ankle edema; Ecg. myocardia damage	Marked	212 117	200 119	...	12 2
38	60	F	2 yrs.	27+	Menopause 24 yrs. ago	Headaches, loss of memory	Loud A2	None	208 117	192 104	...	16 13
39	49	F	3 wks.	56+	Menopausal symptoms for 4 yrs.	Paresthesias (numbness) of left foot	Marked enlargement	Mod.	186 108	186 113	...	..
40	49	M	2 yrs.	3−	....	Dyspnea, palpitation	Moderate enlargement, loud A2, systolic murmur at apex, ankle edema, Ecg. shows myocardial damage	Slight	196 123	195 114	...	..

IN A GROUP OF 40 HYPERTENSION CASES—(*Continued*).

Average reduction with cucurbocitrin.	Laboratory findings.						Symptomatic relief from cucurbocitrin.	Symptomatic relief from liver extract.	Duration of cucurbocitrin therapy, days.	Previous treatment.	Remarks.
	Urine.		Mosenthal test.		Phthalein test.	Blood chemistry mg. per 100 cc.					
	Albumin.	Casts.	Nocturnal polyuria.	Fixation of specific gravity.							
13 2	F.P.T.	0	0	0	60	....	Mod.	Marked	72	None	With double dose no greater effects.
44 16	0	Few hyalin	0	0	50	Urea N. 8.4	Marked	.....	105	Rest	2½ mos. without drug, B. P. 180/110.
23 13	0	0	0	0	55	....	None	.....	52	Luminal	1 week without drug, no relapse.
65 33	F.T.	0	0	5 pts.	55	....	Marked	.....	164	Low salt, low protein; limited fluids, luminal, rest, ovarian extr. pyramidon	2 weeks without drug, no relapse; 6 weeks without drug, B. P. 195/103.
...	F.T.	0	0	0	55	....	Marked	.....	78	Low salt, low protein; limited fluids, luminal, Ki ovarian extract	1 mo. without drug, no relapse.
81 43	F.T.	0	+	0	90	Urea N. 12.1	Comp.	.....	313	Low salt diet	5 mos. without drug, no relapse; 7½ mos. without drug, B. P. 155/90 2 wks. after cucurbocitrin, B. P. again 132/80.
34 11	0	0	+	0	65	....	Mod.	.....	120	Low salt, low protein; luminal, Ki	
43 38	0	0	0	0	35	....	Comp.	.....	120	Low salt, low protein, and luminal, Ki, pyramidon	1 mo. without drug, B. P. 165/60.
31 20	0	0	0	5 pts.	70	....	Mod.	.....	137	Luminal	3 mos. without drug, B. P. 168/100.
30 21	H.T.	Occ. hyalin	0	0	60	....	Marked	.....	93	Low salt, protein and caloric diet	1 mo. without drug, no relapse; Roentgen ray evidence of considerable sclerosis of arch.
28 35	0	0	0	0	65	....	Mod.	.....	21	Low salt, Ki; nitroglycerin, luminal, digitalis	Roentgen ray sclerosis of arch.
28 5	T.	Occ. cellular	0	5 pts.	20	N.P.N. 42.8	Mod.	.....	18	Low salt, low protein, luminal	Hospital patient, in bed 18 days before treatment. Roentgen ray sclerosis of arch.
..	F.P.T.	Occ. granular	..	..	42	Urea N. 15.6 N.P.N. 46.1	None	.....	21	Luminal, ovarian extract	Hospital patient, rest in bed 33 days before treatment.
11 31	F.P.T.	Occ. granular	+	0	70	....	Marked	.....	142	Low salt, low protein; ovarian extract	1 mo. without drug, B. P. 205/80 and headaches.
41 15	T.	0	..	..	59	....	Marked	.....	54	Low salt, low protein	Double dose of cucurbocitrin produced no greater results. Hospital pt. in bed 7 days before B.
10 11	F.T.	0	0	0	65	Urea N. 18.8 N.P.N. 30.1	None	.....	18	Low salt, low protein, KI, luminal	Double dose of cucurbocitrin lowered B. P. by another 26 mm.
12 2	F.T.	0	..	..	..	....	Marked	.....	100	Luminal, digitalis, nitroglycerin, bed, rest	Double dose produced no further improvement. Roentgen ray sclerosis of arch.
16 13	0	0	0	0	50	....	Mod.	.....	40	None	No greater results with double dose.
..	F.T.	0	..	..	..	....	Marked	.....	19	Rest	
..	T.	0	0	0	60	....	Mod.	.....	26	Luminal, digitalis	

TABLE II.—SYMPTOMS ASSOCIATED WITH HYPERTENSION IN OUR SERIES AND THOSE COMPLETELY OR MARKEDLY RELIEVED BY CUCURBOCITRIN THERAPY.

Symptoms.	No. of cases.	Per cent.	No. of cases improved.	Per cent improved.
Headaches	31	80	17	55
Dyspnea	21	55	13	62
Dizziness	16	41	7	44
Palpitation	14	38	8	57
Edema of legs	9	24	4	44
Tinnitus	9	24	4	44
Visual disturbances	9	24	4	44
Fatigue	8	20	4	50
Nervousness	7	19	4	57
Impairment of memory	6	16	1	17
Precordial pain	5	13	4	80
Numbness of extremities	5	13	1	20
Unsteadiness of gait	4	10	1	25
Insomnia	3	8	2	67
Epistaxis	3	8	1	33
Speech disturbances	3	8		
Mental depression	1	3		

The systematized data are presented in the accompanying tables which are largely self-explanatory.

Age. This according to Table III, seems to play some rôle in determining the success of cucurbocitrin in lowering high blood pressure, the successful cases being on the average six years younger than the unsuccessful ones. Also, the average age of patients who failed to get symptomatic relief is five and a half years higher than that of the group composed of cases who did.

Sex. Sex, on the contrary, had no appreciable influence on the outcome of treatment either as to reduction of hypertension or symptomatic benefits.

The Degree of Hypertension. This proved to be of no great consequence so far as the results of cucurbocitrin therapy are concerned.

The Duration of Hypertension. As calculated from the time of detection by instrumental means this appears to have a definite prognostic significance in regard to the symptomatic results of cucurbocitrin therapy. From the same table we see that patients who failed to obtain improvement of their symptoms were known to have had hypertension on the average almost twice as long as the successful cases. This does not hold true when applied to the prospects of blood pressure reduction.

Influence of Body Weight on the Outcome of Treatment. The patients were weighed with their clothes on and their "normal" (not ideal) weight calculated on the basis of sex, height (with shoes), and age, according to tables based on data obtained from the examination of 358,323 American men and women.[3] As can be seen from Table III, the difference in the average weight of the four groups is insignificant, especially in view of the fact that

insurance experts allow 20 per cent above or below as a safe variation from the supposedly healthy average normal weight. Approaching the question of body weight from another angle by segregation of all patients who are 20 per cent or more overweight, we again failed to see any influence of body weight on tractability of hypertension.

Bearing of Kidney Involvement on Results of Treatment. Only six patients in this series were free of demonstrable kidney damage and these six did not respond in a uniform way to cucurbocitrin administration. The outcome of the various kidney tests is correlated in Table IV with the clinical results.

Urinary Findings. A negative urine analysis was found twice as often in patients who responded by lowering of their blood pressure than in those whose blood-pressure remained unchanged. On the other hand, the percentage of negative urinary findings was practically the same in the group of patients showing symptomatic relief as well as in the unrelieved group. Of the individual abnormal constituents of the urine, albumin was found more frequently in patients whose blood pressure remained unchanged, and also somewhat more often in patients who reported symptomatic improvement. On the other hand, casts were found with equal frequency in all groups.

Phenolsulphonephthalein Excretion Test. The success of cucurbocitrin therapy in hypertension is apparently not influenced by the power of the kidneys to excrete dyes, as shown by the average phthalein excretion values.

Blood-urea Nitrogen and Total Nonprotein-nitrogen Determinations. Blood chemistry investigations were carried out in 17 of the earlier cases, but later were discontinued after an analysis of the results showed these had no bearing on the success or failure of cucurbocitrin therapy.

Mosenthal Test. More negative Mosenthal tests were found among the patients whose blood pressure was reduced by cucurbocitrin. Fixation of specific gravity was found somewhat more frequently among the two failure groups. On the other hand, nocturnal polyuria occurred more often among patients who claimed relief from cucurbocitrin medication. However, in no two groups were the differences in the results of the Mosenthal test of sufficient magnitude to permit us to draw any definite conclusions in regard to the possible bearing of vascular nephritis on the success of cucurbocitrin treatment.

Results of Treatment in the Light of Cardiovascular Damage. Quantitative appraisal of organic disease of the heart and blood-vessels is so difficult that only a rough distinction between "marked" and "moderate" involvement of either is attempted below.

Cardiac Damage. Data on which the degree of cardiac involvement was judged are given in Table I. From a percentage analysis of the amount of cardiac involvement in the four groups in Table V,

TABLE III.—INFLUENCE OF AGE, SEX, HEIGHT OF BLOOD PRESSURE, DURATION OF HYPERTENSION, AND BODY WEIGHT ON RESULTS OF TREATMENT WITH CUCURBOCITRIN.

Group of patients.	Average age, years.	Sex.				Average blood pressure before treatment.		Duration of hypertension, years.	Average weight above or below normal, per cent.
		Males.		Females.					
		Cases.	Per cent.	Cases.	Per cent.	Systolic.	Diastolic.		
Blood pressure reduced 10 mm. or more	50.5	9	69	20	74	206	115	4.7	0.9+
Blood pressure unchanged	56.6	4	31	7	26	208	110	4.3	1.9+
Symptomatic relief obtained	50.2	10	77	22	85	205	113	3.6	3.2+
No symptomatic relief	55.6	3	23	4	15	214	119	6.4	6.4−

TABLE IV.—BEARING OF KIDNEY INVOLVEMENT IN HYPERTENSION ON THE SUCCESS OF CUCURBOCITRIN THERAPY.

Group of patients.	Urinary findings.						Average phenol-sulphone-phthalein excretion in per cent.	Average blood-urea nitrogen level in mg. per 100 cc.	Mosenthal test.					
	Albumin.		Casts.		Negative.				Nocturnal polyuria.		Fixation of specific gravity.		Negative.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.			Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more	18	62	7	24	10	34	55.7	15.9	7	26	7	26	16	59
Blood pressure unchanged	9	82	3	27	2	18	54.5	17.0	2	22	3	33	4	44
Symptomatic relief obtained	22	69	8	25	9	28	55.1	16.4	8	28	8	28	15	52
No symptomatic relief	4	57	2	29	2	29	49.5	16.0	1	17	2	33	3	50

it appears that the degree of involvement of the heart when present has no bearing on the success of cucurbocitrin therapy. On the other hand, the absence of cardiac disease is a favorable factor inasmuch as only one patient without demonstrable involvement of the heart failed to obtain lowering of the blood pressure and the symptomatic success of the treatment was universal in all such cases.

Arteriosclerosis. Hardening of the arteries was determined by palpation of accessible arteries, by ophthalmoscopic examination, and by roentgenologic evidence of calcification of the aorta. From Table V it appears that arteriosclerosis has no consistent influence on the outcome of cucurbocitrin therapy when present but that just as in the case of cardiac damage its absence makes for a favorable prognosis. In both groups only one patient without thickening of the arteries failed to respond to treatment.

Significance of the Menopause in Females in Relation to Success of Cucurbocitrin Therapy. Fortunately, over two-thirds of the patients in this series are females and the success and failure of treatment in these were analyzed from the standpoint of onset of hypertension before or after the menopause and also in relation to the menstrual status at the time of treatment. By a casual examination of Table VI one gains the impression that patients with hypertension and regular catamenia respond somewhat better to cucurbocitrin therapy both so far as lowering of the blood pressure and symptomatic relief are concerned. And also that high blood pressure yields more readily in patients in whom the onset of hypertension preceded that of the menopause. However, by a more careful analysis of other possible factors which are known to influence the response of patients to this treatment we find that age and duration of hypertension prior to treatment can readily account for all noted differences. For instance, the average age of patients in the group where hypertension preceded the menopause is 43.7 years while the age of the group in which menopause came on before hypertension is 56.8 years. Similarly the average duration of hypertension in the group with regular catamenia is 2.9 years, while in the group with menopausal symptoms it is 5.7 years, and in the group past their menopause it is five years.

Dosage of Cucurbocitrin and Success of Treatment. As previously mentioned, the standard dose of cucurbocitrin was 50 mg. three times a day. In view of the fact that the immediate fall in blood pressure following a single dose of the drug was in proportion to the size of the dose, larger doses were tried in several patients after their systolic blood pressure had been decreased with ordinary doses by 10 to 41 mm. for some time. Among 7 patients who received 100 mg. three times a day the blood pressure remained unchanged in 5 and in 2 instances it came down further by 10 and 26 mm. respectively without appreciable further symptomatic improvement. In 1 of the 5

TABLE V.—RESULTS OF CUCURBOCITRIN TREATMENT OF HYPERTENSION IN THE LIGHT OF CARDIOVASCULAR DAMAGE.

Group of patients.	Degree of cardiac involvement.						Arteriosclerosis.					
	Marked.		Moderate.		None.		Marked.		Moderate.		None.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more	8	28	16	55	5	17	13	45	11	38	5	17
Blood pressure unchanged	4	36	6	55	1	9	3	27	7	64	1	9
Symptomatic relief obtained	10	31	17	53	5	16	12	38	16	50	4	12
No symptomatic relief	2	29	5	71	..	..	4	57	2	29	1	14

TABLE VI.—SIGNIFICANCE OF THE MENOPAUSE IN FEMALES IN RELATION TO RESULTS WITH CUCURBOCITRIN IN HYPERTENSION.

Group of patients.	Menstrual status.						Onset of hypertension in relation to the menopause.			
	Catamenia regular.		Menopausal symptoms.		Menopause past.		Hypertension before menopause.		Menopause before or with hypertension.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more	6	75	4	67	9	69	10	77	9	64
Blood pressure unchanged	2	25	2	33	4	31	3	23	5	36
Symptomatic relief obtained	7	100	4	67	11	85	10	83	12	85
No symptomatic relief	..	..	2	33	2	15	2	17	2	15

patients the dose was later increased to 150 mg. three times a day without any change in blood pressure or subjective feeling. It is of interest to note here that this was the same patient whose systolic pressure showed an immediate fall of 16 mm. after 50 mg. of cucurbocitrin and one of 26 mm. after 100 mg. of it. The explanation of the failure of larger doses of cucurbocitrin in most instances to decrease blood pressure below a certain level achieved by smaller doses of the drug probably lies in a certain individual minimum of pressure necessary for proper function. Below this level nothing short of shock will reduce the blood pressure for any length of time. Herein seems to lie one of the chief limitations and at the same time a most important safeguard of symptomatic treatment of hypertension.[4]

Untoward Effects of Cucurbocitrin Therapy and the Question of Tolerance. No undesirable effects of cucurbocitrin administration from excessive lowering of the blood pressure or toxic action of the drug were observed in any of the treated patients. In successful cases the same dose of cucurbocitrin was as effective after continuous administration over a period of several months as at the beginning of treatment.

Duration of the Effects of Prolonged Cucurbocitrin Administration. In twenty successful cases cucurbocitrin therapy was discontinued and the patients observed at weekly intervals for rise of blood pressure and return of symptoms. In 12 cases the effects of treatment were known to persist from a week's to a month's time. In 7 cases the benefits of treatment lasted from one to three months, and one patient retained a normal blood pressure and was symptomless for five months.

It is noteworthy that hypertension returned before the appearance of subjective symptoms in 10 cases, whereas the reverse was observed only in 2 patients. An investigation of clinical data having a possible bearing on the duration of the beneficial action of cucurbocitrin brought out the fact that all cases in which hypertension was held in check for one month or more after discontinuation of medication were in women. On the other hand, the group in which the blood pressure began to rise during the first month* included about an equal number of males and females. Parallel with this goes the observation that in 63 per cent of women who responded for longer periods of time the onset of the menopause preceded that of hypertension. On the contrary, in those who benefited only for periods up to one month hypertension preceded the menopause in 83 per cent and in the remaining 17 per cent the discovery of high blood pressure by instrumental means coincided with the first menopausal symptoms, but probably in reality was present earlier. These findings, if confirmed by further observations, would

* Here are also included cases without relapses which could not be followed longer than one month.

mean that more lasting benefits can be obtained by cucurbocitrin in cases of hypertension, the onset of which occurred after the menopause.

Other differences noted between these two groups of patients were that 'phthalein excretion was somewhat higher and cases free from arteriosclerosis were four times as numerous in the group which derived more lasting results from treatment with cucurbocitrin. How great a part in the response of this group can be ascribed to these features, *versus* the onset of hypertension in relation to the menopause, is difficult to say.

Value of Cucurbocitrin Therapy. Cucurbocitrin is a valuable drug in the symptomatic treatment of hypertension because it produces lowering of high blood pressure and gives subjective relief in a large proportion of cases. The desirability of removing, or at least diminishing, the extra load carried by the heart in hypertension is obvious. In addition, secondary vascular-renal degenerative changes may be prevented or their progress slowed down. Symptomatic improvement of many patients under cucurbocitrin therapy was so marked that usefulness and enjoyment of life were restored to those who were practical invalids.

The simplicity of administration and absence of any undesirable effects are additional advantages of this drug.

Results of Cucurbocitrin Therapy Compared to Those of Liver-extract Injections. A complete report of results obtained with liver extract in the treatment of hypertension having appeared elsewhere,[4] we shall limit ourselves here to a brief comparison of the results obtained with these two preparations. From Table VII, in which all cases in both series are compared, it appears that reduction of high blood pressure follows cucurbocitrin therapy in a slightly higher percentage of cases, but that the average lowering of the blood pressure is somewhat greater after liver-extract medication. Symptomatic relief is also obtained slightly more often with cucurbocitrin, while "complete" and "marked" relief of symptoms follows with equal frequency the administration of both drugs. As regards the duration of improvement after either therapy is discontinued, the beneficial results of liver-extract injection appear to last somewhat longer than those of cucurbocitrin medication.

Turning to an appraisal of the two substances in the 21 cases in which they were used consecutively, we see that cucurbocitrin held the ground gained by liver-extract therapy in all but 2 cases and liver-extract administration after cucurbocitrin accomplished the same in all cases except one. In addition out of 14 cases which were treated with liver extract first cucurbocitrin produced an additional lowering of the blood pressure between 15 and 23 mm. in 7 cases. Symptomatic relief over that produced by liver extract was observed from cucurbocitrin in 4 cases. On the other hand, liver extract when given to 7 patients who previously received cucurbocitrin brought

about additional lowering of the systolic pressure of 17 mm. in one case only. Greater symptomatic relief while on liver extract was reported by two and less by one patient in this group of 7 cases.

No direct comparison between the action of the two drugs in these groups can be made, because the group which received liver extract first comprises a greater proportion of failure cases with this method (64 per cent as against 43 per cent of initial failures with cucurbocitrin). However, the success of one preparation after the failure of the other was seen with sufficient frequency to justify a trial with both in refractory cases.

A comparison of individual clinical features making for success or failure of treatment with cucurbocitrin and liver-extract brings to our attention a striking similarity between these two series. With the exception of age, which is unimportant in liver-extract therapy, and duration of hypertension, which in liver-extract cases is significant also in regard to lowering of hypertension, the agreement of all statistical data in the success and failure groups is practically complete.

The above comparisons lead us to the conclusion that outside of minor differences the clinical results of cucurbocitrin and liver-extract therapy are essentially similar, both in kind and degree. The explanation of this must be looked for first in the same pharmacologic action of these drugs which consist of a sustained dilatation of the smallest units of the peripheral vascular system. And, second in their symptomatic rather than etiologic mode of attack on hypertension, which precludes the lowering of high blood pressure below the safe level necessary for adequate function. Both preparations accomplish more in the symptomatic treatment of hypertension than any other methods in the experience of the authors, but the effects of both can extend only so far and no farther, as long as the underlying cause of hypertension is not removed.

Summary. 1. A brief pharmacologic review of cucurbocitrin is given.

2. Examination of patients and the method of administration of cucurbocitrin are outlined.

3. (*a*) The immediate effect of a single oral dose of cucurbocitrin in hypertension cases is a fall in the systolic and diastolic blood pressure. The extent and duration of this fall are roughly in proportion to the dose in the same patient.

(*b*) After prolonged administration of cucurbocitrin in 40 cases of hypertension it was found that a reduction of the average systolic pressure by 10 mm. or more took place in 73 per cent of cases, and that the average reduction of the systolic pressure in these cases was 29 mm., and that of the diastolic pressure 15 mm.

(*c*) Out of 39 cases with symptoms referable to hypertension definite relief was obtained in 82 per cent of cases.

TABLE VII.—RESULTS OF CUCURBOCITRIN THERAPY COMPARED TO THOSE OF LIVER-EXTRACT INJECTIONS.

Treatment.	Blood pressure reduced 10 mm. or more, per cent.	Average reduction of blood pressure.		Symptomatic relief.		Duration of effects.			
		Systolic, mm.	Diastolic, mm.	All degrees, per cent.	Complete and marked, per cent.	Under 1 month.		Over 1 month.	
						Cases.	Per cent.	Cases.	Per cent.
Cucurbocitrin, 40 cases	73	29*	15	82	55	12	60	8	40
Liver extract, 27 cases	63	33	19	76	56	3	37	5	63

* Corrected, see text.

4. The average age of patients who responded to cucurbocitrin therapy was lower than that of the failure group. Sex, the degree of hypertension, and body weight were unimportant. On the other hand, the duration of hypertension prior to treatment was found to be twice as long in the group of patients who obtained no symptomatic relief than in the group that did.

Data in reference to the degree of kidney involvement were not sufficiently decisive to warrant any conclusion.

Cardiovascular damage when present had no consistent influence on the outcome of treatment, but its absence almost always made for a favorable prognosis.

There was no apparent connection between the menopause in female patients and the success of cucurbocitrin therapy save that in all cases in which improvement after discontinuation of the drug lasted for over a month the onset of the menopause preceded that of hypertension.

5. No untoward effects after cucurbocitrin or signs of tolerance to the drug were observed.

6. The effects of prolonged cucurbocitrin administration lasted after the drug was stopped from one week to one month in 11 cases, and from one month to five months in 8 cases.

7. Cucurbocitrin produced lowering of the blood pressure and symptomatic relief in a somewhat larger per cent of hypertension cases than did liver extract's but liver extract reduced the blood pressure to a slightly more marked degree. There also was a striking similarity between the clinical features making for success or failure of treatment with both preparations.

Conclusions. 1. Cucurbocitrin therapy in hypertension causes considerable lowering of the blood pressure, and gives complete or marked relief of symptoms in a majority of cases.

2. Patients under the age of fifty years, with known duration of hypertension of less than three years, and having little cardiovascular damage are most likely to respond favorably to cucurbocitrin.

3. The effects of cucurbocitrin and liver extract in hypertension are essentially alike in kind as well as degree and apparently both are based on sustained peripheral vasodilatation.

BIBLIOGRAPHY.

1. Barksdale, I. S.: Studies on the Blood-pressure Lowering Principle in the Seed of the Watermelon (Cucurbita Citrullus), Am. J. Med. Sci., 1926, **171**, 111.

2. Wilkinson, G. R.: Further Studies on the Blood-pressure Lowering Effect of Cucurbocitrin in Man. Read before the South Carolina Medical Association, Anderson, S. C., April 21, 1927.

3. Gray, H., and Gray, K. M.: Normal Weight. Boston Med. and Surg. J., 1917, **177**, 894.

4. Althausen, T. L., Kerr, W. J. and Burnett, J. C.: Liver Extract in the Treatment of Hypertension, Am. J. Med. Sci., 1929, **177**, 398.

ACUTE LEUKEMIA: A REVIEW OF THE LITERATURE AND OF TWENTY-EIGHT NEW CASES.

By Stafford L. Warren, M.D.,*

ASSISTANT PROFESSOR OF MEDICINE, IN CHARGE OF RADIOLOGY, UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y.

A search of the literature since 1917, when Gorham reviewed 28 autopsied cases of acute myelogenous leukemia, indicates that acute leukemia can no longer be considered a rare disease. The reported cases now number nearly 500. Only 85 cases could be found in this large group which had been proved by autopsy, but there were some cases reported in foreign periodicals which could not be consulted, and it is probable that these would bring the total number of autopsied cases of acute leukemia well up to the hundred mark. I can add to this number 28 new autopsied cases which were treated within the last ten years at the allied hospitals of the Harvard Medical School and at the Strong Memorial Hospital of Rochester, New York. One particularly illuminating case will be cited in detail; while study of the others has influenced the statements made in this paper. Their data have not been included for the sake of brevity.

In this study, acute leukemia is considered as a definite clinical syndrome as distinguished from the two types of chronic leukemia. There is indicated in the discussion the probability that most cases of acute leukemia are of myelogenous origin, but it must be emphasized that a distinction between a lymphogenous and myelogenous origin is often impossible in this acute syndrome. The 28 new cases and those reported in the literature, since 1917, show a wide divergence in diagnoses. Twenty-four per cent were diagnosed as acute myelogenous leukemia, 32 per cent as lymphogenous, 34 per cent as acute leukemia, and 10 per cent as special forms, yet they all followed the usual text-book picture of the acute leukemia syndrome: onset with weakness, a "coryza" or some obscure infection, fever, prostration, bleeding, purpura, adenopathy, splenomegaly, leukocytosis, anemia, immature leukocytes in the blood, leukemic masses and fatal termination.

It is apparent from this that there is no essential difference in the clinical picture of acute leukemia, whether the case has been diagnosed as acute myelogenous or lymphogenous leukemia. The wide divergence in diagnosis in all of these cases of acute leukemia is due to the difficulty in differentiating the immature cell forms so that it is practically impossible to separate the cases into the usual two

* From the Medical Service of the Collis P. Huntington Memorial Hospital, Harvard University, Boston, Mass., and the Department of Medicine (Department of Radiology) School of Medicine and Dentistry, University of Rochester, Rochester, New York.

types. Older immature cells of myelogenous origin, that is, myelocytes, can be recognized by their granules with both polychrome stains and oxydase preparations. Nongranular mononuclears, however, whether lymphoblasts or myeloblasts, do not show oxydase granules and are frequently taken for large atypical or abnormal lymphocytes, though Sabin[15] has shown that at least one type of these nongranular mononuclears is a myeloblast.

Changes in the appearance and number of the white blood cells during the course of the disease may cause further confusion in diagnosis. In many of the cases, at the onset of the disease, the blood smears have shown large numbers of granular myelocytes and a few large atypical nongranular mononuclears. Later this situation has been reversed until, finally, the myelocytes have almost disappeared and the large nongranular forms have predominated. This phenomenon has been described by Reh[14] as acute "myelogenous lymphoid" leukemia, and by Logefeil[10] as mixed leukemia. Ewald, and others,[3] under the title "acute monocyte and stem-cell leukemia," and Lasch[9] ("acute myeloblastic leukemia") attempt to go further upon the basis of morphology alone in recognizing immature cell types. But a comparison of the pictures or plates in the articles of the various authors will convince any critical observer that the differentiation between the immature nongranular cells upon a purely morphological basis is unsafe and perhaps unsound. Myeloblasts cannot readily be distinguished from immature lymphoid cells except by some differential staining method like that used by Sabin;[15] acute cases of about two weeks' duration may have from 60 to 100 per cent of nongranular cells of all sizes and shapes in the blood, varying in number from 1000 to 1,000,000 per c.mm. Sabin[16] points out that there is a variation in size of the myeloblasts "from a cell whose diameter is more than twice that of a red blood cell to one even smaller." Distortion, by smearing and drying of fresh blood or smears from organs, tend further to complicate the picture, and, to the inexperienced observer, the identification of cells becomes extremely difficult. Leukopenia may develop or exist throughout the period of observation of cases of acute leukemia which often leads to diagnostic errors.

The origin of myelocytes and the differentiation of the younger types of these cells are still in controversy and beyond the scope of this report. The stages of this controversy can be traced in the predominance of a certain diagnosis over a definite period of time. Up to 1910, acute myelogenous leukemia was more frequently diagnosed than lymphogenous, and the nongranular cells were called myeloblasts. Then there was a period of doubt for the next ten years, when for the most part, strictly similar cases were called lymphogenous, the nongranular cells being called lymphoblasts, and the myeloblasts either ignored or forgotten. Now the clinician and the pathologist are more cautious and are apt to make the diagnosis

simply that of acute leukemia with qualifications. Probably within the next five years, myelogenous leukemia will be thought more frequent than the lymphogenous type.

Autopsy findings in the gross help little to determine the origin of the disease as there is obvious splenic, lymph-node, and bone-marrow involvement in varying degree in all cases. On microscopic examination of the tissues, it is usual to find all of the organs infiltrated with leukemic cells, frequently in numbers large enough to cause atrophy of the normal structures. One is often at a loss to differentiate these cell types because the morphology is no more distinctive in the tissues than in the blood stream; thus the pathologists usually avoid the issue and state that the cells resemble lymphocytes or myeloblasts, and the like.

Ewing[4] emphasizes that "the lesions of leukemia, both lymphocytic and myelocytic, involve the bone marrow, lymph nodes, spleen and other preëxisting lymphoid tissues. The picture is that of a diffuse *systemic* involvement of blood-forming organs with secondary invasion of other tissues."

Different pathologists classify the same leukemic-cell infiltrations or "leukemic" masses under such different terms as leukoblastoma, myeloblastoma, leukosarcomata, lymphomata, lymphoblastomata, malignant lymphomata, and so forth, each term reflecting a slightly different idea of the origin of the cells involved. Others have classified, in special groups, those cases with lesions or masses in certain specific regions although the location of the lesions does not necessarily indicate a difference in etiology; that is, "Sternberg's leucosarcomatosis" for a leukemia with a mediastinal leukemic mass.

In the survey of the reported and the new cases, the general impression was obtained that the leukemic process brought about a generalized infiltration of the organs by the leukemic cells, and the lesions were rather stereotyped. Certain unusual manifestations, however, are of particular interest. Osler, in 1892, recorded nodular masses of leukemic cells in the base of the tongue, the stomach mucosa, and the lung parenchyma; otherwise these do not seem to have been noted in the literature. Nodules in the skin have been reported by Ward,[17] Joachim,(1917) and others though they are relatively uncommon. Four of the 28 new cases reviewed here had leukemic nodules in the skin as a prominent feature. There were 2 cases with nodules in the lungs, 4 cases with extensive central nervous system infiltration accompanied by fatal cerebral hemorrhage, 3 cases with large nodules in the heart, and 2 cases with large mediastinal masses (Sternberg's type). One case, a boy, aged nine years, was found to have nodules in all of his organs, and in addition such an extensive and massive infiltration by the leukemic cells as to make up quite an appreciable part of his total body weight. From one-third to one-half of every section taken was composed of these atypical, immature, nongranular cells. Retroperitoneal masses were also not uncommon.

For the purposes of analysis of these cases, the onset of the disease is arbitrarily taken from the first symptom obviously due to the leukemia. The leukemic process probably had been present for some time before this was manifested. The duration of the disease is indicated in Chart I. The sharp grouping of 84 per cent of the

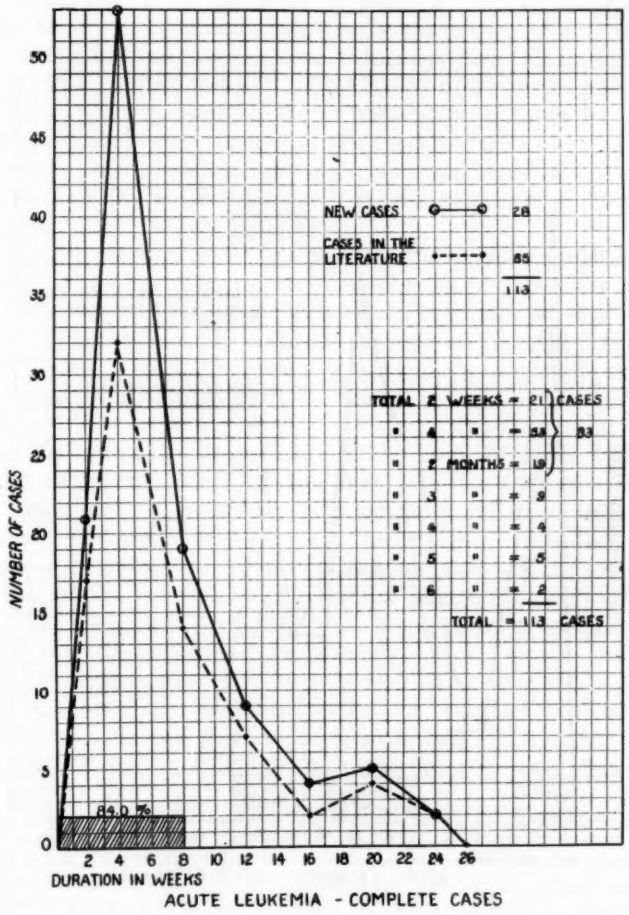

NEW CASES 28
CASES IN THE LITERATURE 85
113
TOTAL 2 WEEKS = 21 CASES
" 4 " = 38 83
" 2 MONTHS = 19
" 3 " = 8
" 4 " = 4
" 5 " = 5
" 6 " = 2
TOTAL = 113 CASES
84.0 %
NUMBER OF CASES
DURATION IN WEEKS
ACUTE LEUKEMIA - COMPLETE CASES

CHART I.—Showing the duration of the illness of 113 autopsied cases of acute leukemia.

cases within the first eight week period is very striking. Of the total of 113 cases of acute leukemia (85 reported in the literature since 1917 and 28 new cases reported here) 21 (18.5 per cent) died within two weeks after the onset of the acute symptoms, showing the devastating effect of the process once it is under way. These

figures agree with those reported by Minot and Isaacs[12] and Ward[17] who analyzed the cases upon the basis of the clinical diagnosis only.

A study of the age incidence of the 113 cases (Chart II) reveals that the disease is particularly apt to occur at three different periods in life; namely, up to ten years of age (24 per cent), between 25 and 35 (42 per cent), and between forty-five and fifty years of age (20 per cent).

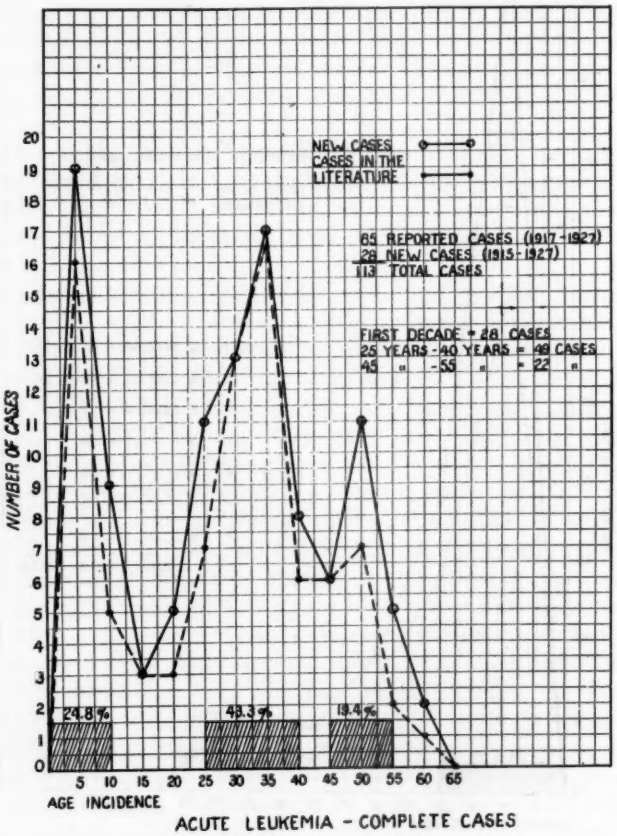


CHART II.—Showing the age grouping of the autopsied cases of acute leukemia.

Acute leukemia seems to be a disease of *males*. They predominate in a ratio of almost 2 to 1, throughout. Among the cases lasting for less than two months (Chart I) 61 per cent occurred in males and of those patients who had the disease for three to six months, 76 per cent were males. Of the patients under ten years of age, 69 per cent were males and 61 per cent of the patients between twenty-five and thirty-five years of age were males. On the contrary between

the ages of forty-five and fifty years, there are 8 females and 3 males, a ratio of about 3 to 1, which indicates a predilection of the disease for *females* at the *menopause period*, as in both of the other groups, two-thirds of the cases occurred in males.

In summarizing information concerning the prodromal period, many apparently unrelated symptoms may be the first symptoms of acute leukemia. There are, however, three very common complaints which stand out as predominant early symptoms of this disease. The patient frequently consults a throat specialist because of sore throat and enlarging tonsils. If the leukemia is unrecognized, the tonsils may be removed. This is frequently followed by severe, prolonged hemorrhage because of the marked decrease of the blood platelets. Thirty to 40 per cent of the patients have had a prolonged hemorrhage after tonsillectomy, dental extraction, or some trifling operation leading to exsanguination.

Ulcerative stomatitis is frequent in the early stages of acute leukemia, the ulcerative lesions involving the pillars of the tonsils, the tongue, and the posterior pharynx. The organisms of Vincent's angina (bacilli and spirilli) occurred in about 50 per cent of the cases under review. In nonleukemic cases, such a stomatitis may be accompanied by a blood picture roughly resembling that of acute leukemia.

In somewhat over 50 per cent of the cases of acute leukemia, shortly before the onset of the first symptoms attributable to leukemia, there was a history of respiratory infection, sometimes classified as a "cold," "the grippe," "bronchitis," or the like. This infection is recorded usually as "hanging on" and "failing to respond to treatment." There is usually more prostration than there is reason to expect, and the severity of the symptoms remains unexplained until the leukemia is recognized.

The following case is briefly summarized as the most unusual of the group because of the nodules in the skin, stomach mucosa, lung parenchyma, and retroperitoneal regions, and the absence of any extensive hemorrhage. The blood was studied in great detail.

Case Report. A woman, aged fifty-six years, for three months, had had a series of "colds" and a feeling of weakness. The past history has no bearing upon the present illness. Two weeks previous to entry, hoarseness and aphonia developed. One week later, a crop of "small lumps" suddenly appeared in the skin over the chest and abdomen "almost in a day." The spleen was not palpable, and a white blood-cell count then was 70,000 per c.mm. The patient rapidly became weak and stuporous and was sent into the hospital.

On admission the patient was semicomatose; temperature 100.4° F. The skin was darkly pigmented and did not show pallor. There were several petechiæ over the shoulders and the buttocks. Many discrete nodules were found in the skin over the chest, abdomen, and back. They varied from 1 to 6 mm. in diameter, were slightly elevated, were lilac or pinkish in color, and seemed confined to the skin or superficial tissue. The tonsils were large and red but not ulcerated. The submaxillary lymph nodes were

the only lymph nodes palpable. The spleen was felt 4 cm. below the left costal margin, firm, not tender. The liver was palpable 4 cm. below the right costal margin. The rest of the examination was essentially negative.

Blood findings were as follows: Hemoglobin 65 per cent (S); red blood cells 2,900,000 per c.mm.; white blood cells 180,000 per c.mm., of which 90 per cent were atypical, nongranular mononuclears. The blood platelets were markedly diminished.

The urine was positive for Bence-Jones protein.

The next day, the patient was irrational, oozing of blood occurred from the gums, new ecchymoses appeared, and there was an increase in the size of the lumps in the skin. The skin was waxy in appearance. A generalized adenopathy of small discrete nodes was noted. The spleen increased in size and was palpable for 8 cm. below the ribs, almost level with the iliac crest. It seemed to have doubled in size within twenty-four hours. The liver remained unchanged. The white blood cells were 141,700 per c.mm.

The spleen was irradiated in an attempt to aid the patient temporarily. Eight hours after the radiation all bleeding from the gums had stopped and the spleen had decreased to about half of the previous size. The patient became stuporous, and exitus occurred twelve hours after the radiation had been given, without further changes being noted, though the patient was frequently examined.

Laboratory Data. Blood withdrawn by vein puncture was gravish-brown and viscous and, added to powdered potassium citrate, became stringy and rubbery before it could be centrifuged; no definite firm clotting occurred at any time. No clot retraction occurred even after one month's time. The bleeding time averaged from five to fifteen minutes. In a blood smear, when the white blood count was 141,700 per c.mm., the white blood cells seemed almost equal in volume to the red blood corpuscles. Three differential counts of white cells stained with Wright's stain on each of three days averaged: Neutrophilic polymorphonuclears, 2 to 7 per cent; young neutrophilic polymorphonuclears, 2 to 7 per cent; small normal lymphocytes 3.5 to 6 per cent; neutrophilic myelocytes 8 to 12 per cent; eosinophilic myelocytes 8 to 12 per cent; large (nongranular) myeloblasts (Figs. 1 and 2, identified by Sabin's vital staining technique) 54 to 66 per cent; medium sized nongranular mononuclears, larger than small lymphocytes, 13 to 20 per cent. Peroxydase blood smears (Goodpasture's stain) showed 8 to 12 per cent of fairly large cells with large numbers of small granules packed around an indistinct oval or kidney-shaped nucleus and 4 to 7 per cent of similarly shaped cells with one to six rather large granules. There were many cells of similar appearance without any oxydase granules. The total percentage of mature cells and myelocytes demonstrated with the Wright's and supravital stains varied from 14 to 25 per cent, so that the discrepancy between these two methods is not marked insofar as the identification of fairly mature cells is concerned.

The red blood cells showed marked anisocytosis and poikylocytosis, a moderate amount of achromia, and occasional polychromatophilia. Microcytes were rare. Nucleated forms were seen occasionally. Blood platelets were few, small, and poorly stained.

Clinical Diagnosis. Acute leukemia, probably myelogenous. Probable duration three months, although definite symptoms occurred for only about four weeks.

Autopsy. (Dr. William McNamara.) The body was that of a well-developed and nourished middle-aged white female. The skin of the entire body was studded with small, purplish tumor masses, the largest being about one-half centimeter in diameter. All the superficial lymph nodes were palpable, several in the neck being enlarged to 3 cm. in diameter. Two distinct tumor masses were felt in the abdomen. The tonsils were enlarged and of a dark-purple color. Numerous purplish masses were seen

FIG. 1.—(Oil Immersion) (Untouched microphotograph of blood smear stained with Wright's stain.) One neutrophilic myelocyte is at the top with a medium sized, nongranular mononuclear beneath it. At right, near bottom, is a large nongranular mononuclear identified by supravital stains as a myeloblast, Sabin's type A. Three other medium sized mononuclears are below and to the left of this.

FIG. 2.—(Oil Immersion). Untouched microphotograph of blood smear stained with Wright's stain. The small dark cell resembles a small lymphocyte. The remaining four cells are large, nongranular, mononuclears identified as myeloblasts by supravital stains.

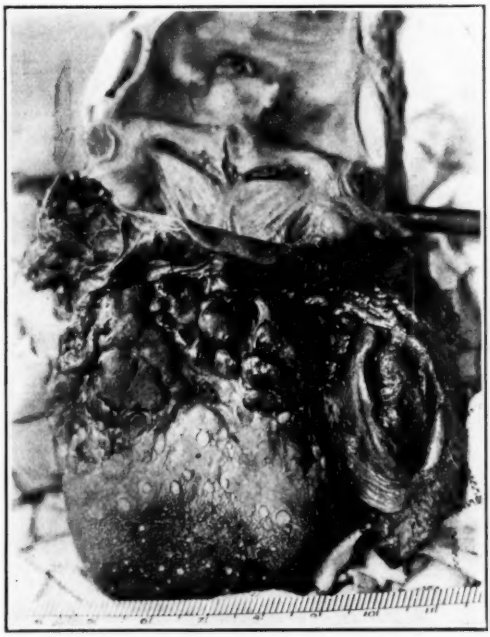


FIG. 3.—The dark, purplish, leukemic masses in the tonsillar ring.

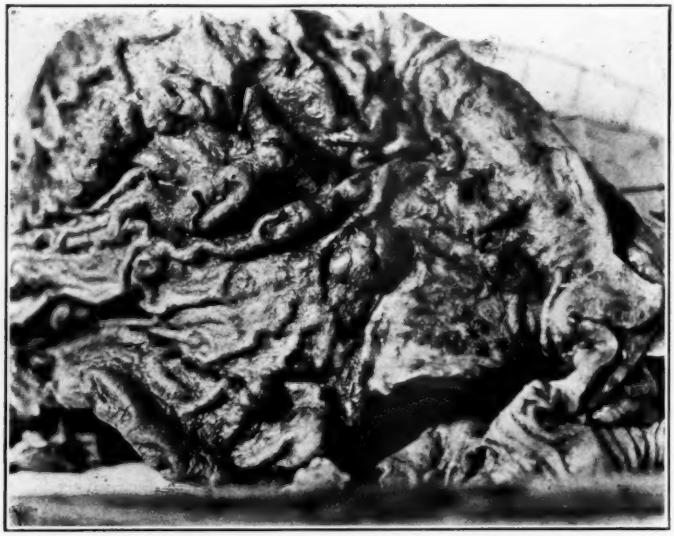


FIG. 4.—There are six large, dark, purplish masses from 1 to 1.5 cm. in diameter and many (50 or more) from 2 to 4 mm. in diameter spread over the stomach mucosa. These are composed of leukemic cells.

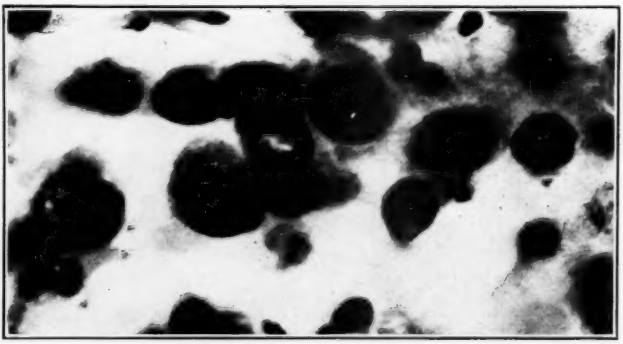


FIG. 5.—(Oil Immersion). Section from a small tumor mass in the liver (Hematoxylin-eosin stain.) In the middle of the picture from the left edge to the right is a series of cells apparently young myelocytes and myeloblasts. The nuclei are large, round, or oval and the cytoplasm is voluminous and slightly basophilic and without granules. The smaller cells suggest lymphocytes. The larger resemble the myeloblasts and myelocytes found in the peripheral blood.

on the posterior portion of the tongue in the tonsillar ring (Fig. 3). When the abdomen was opened, two tumor masses were seen, one in the retroperitoneal tissues, measuring about 8 by 4 by 4 cm.; the other situated in the omentum, measuring 3 by 4 by 4 cm. Both were of a cherry-red color. On cut-section these tumors presented a soft, purplish, homogeneous, pulpy surface from which very little blood exuded. All the abdominal lymph nodes were enlarged and purplish-gray in color on section. The spleen extended down to the costal margin. The pleural cavities contained no excess of fluid. Nothing was noted superficially except the dark-purplish color of the lungs and the numerous purple areas studded throughout the pleura.

The lungs were heavier than normal. Both were air-containing and, on cross-section, showed numerous small purplish pectechiæ and purplish nodular areas about 2 to 5 mm. in diameter which were thought to be due to leukemic-cell masses.

In the kidneys and the liver, no gross lesion could be seen, though a grayish-white infiltration seemed present throughout these organs with some distortion of the normal architecture.

The spleen weighed 400 gm. and was quite firm and bluish in color. There were no adhesions to its surface. On cross-section, the pulp was soft and purplish and scraped off readily. The Malphigian corpuscles and the normal structure were poorly defined due to an increase in pulp substance.

The stomach mucosa was studded with dark, purplish-blue, tumor masses about fifty in number, the average being about 3 mm. in diameter. There were several larger masses of about 1.3 cm. in diameter in the antrum. These tumors were were all umbilicated and the larger showed some superficial ulceration (Fig. 4). On cross-section, they were firm, homogeneous, and dark purple in color. Very little blood exuded from them. There were a few similar nodules in the lower intestinal tract, not related definitely to the lymphoid structures.

The bone marrow of the center of the femur and the ribs was dark red, gelatinous, and extremely cellular. The ribs were thin and cut easily as if osteoporosis had occurred.

The remainder of the organs showed no gross abnormality related to the leukemia.

The most interesting aspect of this case was found in the microscopic study of the leukemic cells and their distribution. There was a general infiltration of every organ examined, by leukemic cells which resembled the small lymphocyte in size and shape but possessed a more abundant cytoplasm which stained pink with hematoxylin-eosin. Some of these cells had a nucleus very similar to that of a myelocyte (Fig. 5), but no granules were seen in the pinkish cytoplasm. There were no granules in similar cells which were thought to be myeloblasts. Oxydase granules did, however, occur in many of the cells from smears of the various organs. The following percentages of cells contained oxydase granules, and they probably were myelocytes: Bone marrow, 80 per cent; spleen, 40 per cent; liver, 10 per cent.

The peculiar purplish or grayish appearance found in the lungs, liver, kidney, stomach and other organs was caused by neoplastic-like infiltration by this large nongranular mononuclear cell (Fig. 5) which apparently is a myeloblast or primitive cells of bone-marrow origin. The various cells found in the organs are shown in Fig. 5, and their appearance suggests a transition of some form of primitive cells to early forms of myelocytes. The bone marrow of the center of the femur and the normally inactive parts of the ribs which were extremely cellular contained only cells in a more or less embryonic state. The predominating cells seemed identical to the primitive cells in the blood cells thought to be myeloblasts, though a few myelocytes were found in most of the sections.

There was another type of cell found only in the two large, cherry-red abdominal tumors. This cell was similar in all of its characteristics to an erythroblast. It was much larger than the predominating cell of the other tumors. The cytoplasm stained a faint red with hematoxylin-eosin but was nongranular, and the nucleus was small and dark. In some instances, the nucleus was seen to be partly extruded. The cells contained iron as demonstrated by special stains, so that apparently these cells were some early form of an erythrocyte containing hemoglobin.

Autopsy Diagnosis. Acute leukemia—probably myelogenous (primitive-cell type) with masses of leukemic cells infiltrating all of the body tissues.

Discussion. With the oxydase stain, then, the myelogenous cell types have been traced back to a nongranular cell resembling a large lymphocyte but with more cytoplasm than large lymphocytes have and with either a round or an indented nucleus. There was also an undifferentiated cell type smaller than this with a relatively large amount of cytoplasm and no oxydase granules.

Two explanations offer themselves. Either this later cell is the originator of all myelogenous cells, which, by virtue of the overwhelming demand for cells, is thrown out into the circulation in its primordial state; or, due to the same urge, lymphoblasts are stimulated to multiplication and are thrown out before maturation. Against the latter, though not proof, is the lack of balance in numbers between lymphogenous and myelogenous cells in the smears. No cells could be positively identified as normal, mature, large lymphocytes. Except for the cells containing oxydase granules, the blood cells, in this case, are difficult to tell from those of the acute lymphatic leukemia, except by the supravital staining technique, and even then certain doubt arises concerning the status of exceedingly primitive stem cells.

Dr. C. A. Doan very kindly studied several live-blood preparations from this case, using the supravital staining technique, and demonstrated the neutral red granules in the large, immature cells which were nongranular with Wright's stain and which showed no peroxydase granules. It was his opinion that these cells were myeloblasts and similar to those described by Sabin and Doan and others[16] in a case of chronic myelogenous leukemia in an acute phase.

Since the autopsy disclosed cells of an undifferentiated type packed in every available space in all of the body tissues and since cells resembling erythroblasts were likewise noted, this would seem to indicate that it was a primitive or "stem" cell with the ability to differentiate into several types, and seems to offer some support to the theory of the single-cell type as an origin for all blood cells. It also suggests a neoplastic process because very malignant tumors commonly revert to very simple undifferentiated cell types or in extreme instances to differentiate toward one- or several-cell types. The pathologist, in trying to differentiate these cases by the morphology of the cells, is almost as much at sea as the clinician, especially in differentiating the immature-cell types.

The cases under review here showed evidence of a wide disagree-

ment as to the classification of similar cell types. The cells in the blood and tissues usually have been classified strictly from their morphologic appearance, and the opinion and diagnosis of the clinician has seemed in many cases to have influenced the pathologist in his classification. The late Dr. J. Homer Wright (personal communication) has called these abnormal immature cells "bastard cells" in that they defy classification at present. It is possible that, in the acute leukemias, the cells predominating are thrown out before they have been able to mature and differentiate. If the "single-cell" theory is correct, there may be no possibility of separating some of the cases of acute leukemia into such types as are clearly defined in the chronic cases.

Until hematologists and pathologists come to an agreement upon blood-cell types and their origin, and this presupposes that we have a simple, differential method of recognizing these types, the differential diagnosis between different types of acute leukemia will be difficult to make. The supravital staining technique,[16] if it is more generally used, would demonstrate that usually in acute leukemia the mononuclear cells are myeloblasts occasionally monocytes and seldom lymphocytes. Apparently most of the acute cases on record that have been diagnosed as lymphogenous could just as well be called myelogenous leukemia or *vice versa*, because there is no definite difference between them in the onset, progress, signs and symptoms, blood findings (without the supravital technique), and autopsy descriptions. There are differences in degree only. In both types of leukemia, the abnormal cells infiltrate all the organs to a varying degree. The diagnosis depends entirely upon the cell type in the circulating blood and in the tissues. Cell masses (lymphomata) may occupy the lymph nodes, the region of the thymus, the retroperitoneal structures, and the various organs, much in the manner of a neoplasm. The duration is so short and the stimulus to produce cells so great that the appearance of the cell masses is decidedly neoplastic. The process concerns an atypical, primitive, or embryonic cell-type which is acting much like a neoplasm so that all of the various primitive and atypical forms are to be seen in the tumors or cell masses.

As a general rule for the present, it may be wiser, in the clinic, to disregard the precise classification of these very immature cells in the cases of acute leukemia until their status is more definitely settled and to avoid confusion and fruitless discussion by recognizing only the primitive nature of the predominant cells.

Conclusions. From 113 autopsied cases of acute leukemia, (85 reported in the literature since 1917 and 28 new cases reviewed here) the following conclusions can be drawn:

1. Acute leukemia is not a rare disease.
2. The constancy of the history, course, clinical, blood and tissue findings in acute leukemia is noteworthy, regardless of whether the case is considered to be of myelogenous or lymphogenous origin.

3. Acute leukemia is essentially a disease of infant and young adult males, but in the fourth decade of life (menopause period), females are more frequently involved.

4. The duration is short. Eighty-four of the 113 cases died within two months after the onset of symptoms clearly due to the leukemia.

5. Acute leukemia of myelogenous origin frequently is diagnosed incorrectly as lymphogenous in type because the primitive bone-marrow cells are mistaken for lymphocytes. Supravital stains aid in distinguishing the type of leukemia.

6. A case with unusual nodules in the stomach mucosa, skin, tongue, and lungs is described.

NOTE.—I wish to express my appreciation of the kindly assistance and criticism given by Dr. George R. Minot, who was my Chief of Service at the time this study was being made.

BIBLIOGRAPHY.

1. Downey, H.: Arch. Int. Med., 1924, **33**, 301.
2. Downey, H., and McKinlay, C. A.: Arch. Int. Med., 1923, **32**, 82.
3. Ewald, O., Frehse, K., and Hennig: Deutsch. Arch. f. klin. Med., 1922, **138**, 353.
4. Ewing, J.: Neoplastic Diseases, W. B. Saunders Company, Philadelphia, 1919, p. 338.
5. Gorham, L. W.: Albany Med. Ann., 1917, **38**, 201.
6. Herz, A.: Wien. klin. Wchnschr., 1926, **39**, 835.
7. Joachim, H., and Loewe, L.: AM. J. MED. SCI., 1927, **174**, 215.
8. Landon, J. F.: AM. J. MED. SCI., 1925, **170**, 37.
9. Lasch, F.: Wien. klin. Wchnschr., 1925, **36**, 777.
10. Logefeil, R. C.: Arch. Int. Med., 1924, **33**, 659.
11. Ludke, H.: Deutsch. med. Wchnschr., 1920, **46**, 345.
12. Minot, G. B., and Isaacs, R.: Boston Med. and Surg. J., 1924, **191**, 1.
13. Richter, M. N.: Arch. Int. Med., 1925, **36**, 13.
14. Reh, T.: Arch. d. mal. du coeur, 1921, **14**, 167.
15. Sabin, F. R.: Physiol. Rev., 1922, **2**, 38.
16. Sabin, F. R., Austrian, C. R., Cunningham, R. S., and Doan, C. A.: J. Exper. Med., 1924, **40**, 845.
17. Ward, G. R.: Proc. Roy. Soc. Med., 1912, **5**, med. sec., 73.

SYSTEMIC RELAPSES DURING LIVER INDUCED HEMOPOIETIC REMISSIONS IN PERNICIOUS ANEMIA.*

BY RAPHAEL ISAACS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF MICHIGAN; ASSISTANT DIRECTOR, THOMAS HENRY SIMPSON MEMORIAL INSTITUTE FOR MEDICAL RESEARCH, ANN ARBOR.

(From the Thomas Henry Simpson Memorial Institute for Medical Research of the University of Michigan, Ann Arbor.)

PERIODICITY of relapses and remissions is characteristic of many diseases. It is noted in purpura hemorrhagia (thrombopenic), arthritis, malaria, asthma, hay fever and related diseases, diabetes,

* Read before the Central Society for Clinical Research, Chicago, November 23, 1928.

nephritis, as well as in other conditions. The seasonal recurrence of common colds and bronchitis is a well-established clinical observation. The periodicity in pernicious anemia is an outstanding feature and has been the subject of much study. The relapses in this disease have usually been described as accompanied by changes in the blood. The production of remission by means of liver[1] or an effective liver extract[2,3] has enabled us to throw new light on the nature of this variation as well as of the disease as a whole. The liver-induced remission differs from the spontaneous remission in that the latter is rarely complete, especially in the return of the red blood-cell count to normal. The liver-induced remissions have enabled us to study patients whose blood cell count has reached 5,000,000 red blood-cells per c.mm. and to note what other symptoms and signs have appeared and disappeared with the return of the blood to normal. Previous to this it was often assumed the residual symptoms were the result of the incomplete hematopoietic remission.

Eighty consecutive pernicious anemia patients were studied at this institute, and records were compiled of 304 relapses, of which there was an adequate description. These patients had more relapses, but only those of which definite data was obtainable were included in this study. Of these, 166 recurred in the same season as a previous relapse in the same patient. Thus, if a patient had his first relapse in October and another relapse was in September, October or November, it was classed as in the same season, the term "season" not necessarily referring to winter or summer, but more nearly to the group of months. This means that, although the relapse could have occurred in four possible groups of three months, 54.6 per cent of the relapses occurred in the same group of months. A patient may, then, expect a relapse, or symptoms of it, more frequently in the same group of months as previous relapses have occurred rather than at a new time of the year.

Although the relapses are usually considered as accompanied by a group of symptoms, it has been found that many of these symptoms appear in patients with liver-maintained remissions, even though the blood count remains normal. These patients may show, at intervals, ease of fatigue, glossitis, gastrointestinal symptoms, nausea, loss of appetite, weakness, nervousness, diarrhea, constipation and increase in numbness and tingling of hands and feet. These "abortive relapses" correspond often to relapses on the part of *other* systems than the blood, and show the inherent tendency of the disease to exacerbations. A loss of appetite during one of these relapses frequently causes a patient to discontinue the liver therapy with the development of a hematopoietic relapse in from four to eight weeks. If liver therapy is not interrupted the symptoms may subside and the blood relapse not appear. The onset of the relapse with loss of appetite may account for the discontinuance of the liver rather than the discontinuance of the liver result in the relapse.

Some patients, however, stop eating liver because they feel perfectly well and do not appreciate the importance of its continuance. These patients may continue for months without a blood relapse. The outstanding feature which has developed from the study of the liver-induced remission is that a remission or a relapse may affect one system and not another, such as the blood and not the nervous system, or the digestive system at another time than the blood. The liver-induced remission is primarily a blood and secondarily a gastrointestinal remission. The loss of appetite may disappear while the patient is taking liver or a liver extract and may also reappear while the blood is normal and while the liver is still being taken. Glossitis may persist or reappear and the achlorhydria does persist. Cutaneous manifestations may improve (decubitus ulcer) or may remain (gray hair). The bone-joint symptoms appear to be entirely independent of the symptoms on the part of other systems. These consist of pains in the joints, stiffness on changing position, pain and tenderness in the bones. There may be an associated atrophic or hypertrophic arthritis. In a relapse one type of symptom may predominate, such as diarrhea, glossitis and abdominal distress. There appears to be no relation between the red blood-cell count and the subjective symptoms. While dyspnea, edema and fatigue may be present with a very low count, they may also be absent while activity is restricted. Some of our patients have been prostrated with a red blood count of 3,000,000 red blood cells per c.mm., whereas others walked about and appeared to show no great discomfort when the red blood count was 1,000,000. Several patients resumed normal activities with a red blood count of 3,000,000, and this apparently was "normal" for them. There is a marked change in subjective symptoms two to three days after liver or liver extract is begun before there is any demonstrable change in the total red blood.

The following types illustrate certain forms of relapses, with and without anemia:

1. **Periodic "Symptomatic" Relapses with "Blood" Relapse.** This is the most commonly described type of relapse, in which the patient tires easily, shows a loss of appetite and a blood study shows anemia. It is quite probable that in many, if not most of these patients, the symptoms precede the anemia. In the average patient, however, the blood is rarely studied when the first symptoms are noticed and a period of weeks to months elapses before the diagnosis is made. This is especially true of the first relapse or the onset, and, unless the patient is followed carefully, is equally true of the subsequent periods.

2. **Periodic "Symptomatic" Relapses, without a Concomitant Change in the Blood Picture.** (*a*) *When the Blood Count is Normal.*

Case Reports. CASE I.—The patient (164077), a woman, aged sixty-one years, had had two relapses previously. In March, 1927, she was in

a relapse and a "liver remission" was induced. She discontinued the liver diet and in November, 1927, developed another relapse. The following data give the subsequent course:

November to December, 1927: "Liver remission."

February, 1928: Tired; not as vigorous as in last month. Red blood cells, 5,100,000 per c.mm.; hemoglobin, 67 per cent. (Sahli.)

March, 1928: Tires easily; loss of appetite. Red blood cells, 4,100,000 per c.mm.; hemoglobin, 69 per cent. (Sahli.)

The ease of fatigue and loss of appetite, although the blood count was within normal limits, were significant as subsequent events showed.

April, 1928: Red blood cells, 3,800,000 per c.mm.; hemoglobin, 67 per cent. (Sahli.)

May, 1928: Not doing well; ease of fatigue; sore tongue. Red blood cells, 3,600,000 per c.mm.; hemoglobin, 81 per cent. (Sahli.)

July, 1928: "Complete" relapse. Red blood cells, 2,800,000 per c.mm.; hemoglobin, 84 per cent. (Sahli.)

August, 1928: "Liver remission." Red blood cells, 4,700,000 per c.mm.; hemoglobin, 91 per cent. (Sahli.)

October, 1928: Appetite lost; tires easily. Red blood cells, 3,500,000 per c.mm.; hemoglobin, 61 per cent. (Sahli.)

In this patient the ease of fatigue and loss of appetite made her disinclined to follow her liver diet or to take liver extract after a remission had been induced and was being maintained. Nevertheless, the symptoms developed while she was taking liver or an effective extract, and she did not have the will power to force the diet at this time.

CASE II.—This patient (170347) illustrates a similar point. After a severe relapse a remission was induced by a liver extract and the patient then ate ½ pound of liver daily. She felt well and her condition returned to normal and remained so for almost a year, when she lost her appetite. She tried to continue with the liver, but found it impossible. Then she developed weakness, and, with the onset of anemia, showed pallor, dyspnea and palpitation. Neurologic symptoms (difficulty in walking) had developed steadily during the blood remission.

CASE III.—This patient (165879) had a liver remission in April, 1927, and he ate an adequate amount of liver daily. In September his red blood-cell count was 4,250,000 per c.mm., and his hemoglobin was 80 per cent. (Sahli.) At this time he was having progressive difficulty in walking and increased numbness in his legs, symptoms which began a month before. He felt "weak," "dragged out" and was suffering from "gas." During the next three months his blood count remained normal and he received an effective liver extract daily. His neurologic symptoms progressed and the fatigue became more marked, even though his blood count in December was 4,730,000 red blood cells per c.mm. and his hemoglobin 85 per cent. (Sahli.) He became weaker, lost his appetite, discontinued his liver and liver extract (a commercial preparation which proved to be ineffective) which he was taking at that time, and a complete hematologic relapse developed in March, 1928.

(b) Accentuation of Symptoms of Relapse or the Appearance of New Symptoms when the Blood Count is Practically Stationary, but at a Low Level.

CASE IV.—(148836.) A woman, aged sixty-one years.

July, 1925: Numbness of hands and feet and weakness.

December, 1925: Burning sensation of hands and feet.

January, 1926: Sore tongue.
April, 1926: Fainting spells.
June, 1926: Lost power to walk. Ankles "gave way."
July, 1926: Lost position sense in her feet and legs.
January, 1927: Loss of control of bladder.
October, 1927: Loss of control of anal sphincter.
December, 1927: Decubitus ulcers.

During this period the blood counts varied between 2,500,000 and 3,500,000 red blood cells per c.mm. The progressive advancement of the spinal-cord lesions accounts for the development of new symptoms in this patient. Subsequently this patient received large doses of an effective liver extract, with improvement in her blood and a lessening in the severity of her neurologic symptoms.

(*c*) *Symptomatic Relapses during Period of Relative Polycythemia.* Christian[4] pointed out that after a patient had become accustomed to a low red blood-cell count he would have a relative polycythemia when his erythrocyte count reached 5,000,000 per c.mm. The following are some of the symptoms noted in patients when the blood counts became normal. The symptoms were new in some cases, in others they were the reappearance or exacerbation of old ones. Many patients, however, with red blood-cell counts of 5,000,000 or over, experienced no symptoms for months.

TABLE I.—SYMPTOMS NOTED WHEN BLOOD COUNT BECAME NORMAL.

Patient.	Red blood cell count, millions.	Hemoglobin, per cent.	Symptoms.
1	5.98	81	Sore tongue.
2	5.01	82	Sore tongue; dizziness on stooping or turning head rapidly.
3	6.76	85	Nausea; development of "numbness" in fingers.
4	6.06	91	"Peculiar sensation in head."
5	5.60	97	Sensation of warmth and coldness in hands.
6	5.50	77	Sore tongue.
7	5.80	74	Ease of fatigue.
8	5.20	91	Dizziness, palpitation, vertigo.
9	5.02	73	Feeling of fullness in head; dizziness.

3. **Symptomatic Remissions.** While it is not surprising that there should be an alleviation of symptoms when the blood count is normal or nearly so, a remarkable symptomatic improvement appears during the first week of liver therapy, before there is a significant change in the red blood-cell count. A sense of well being appears, a change in mental outlook, a loss of anorexia, nausea and vomiting, improvement in the bowel movements, lessening of ease of fatigue and increase in muscular power (subjective). The psychic "remission" is one of the most marked of any change in medicine. A depressed, apathetic patient, with no appetite, little interest in surroundings and even antagonism to those about him, becomes, within three to five days, a keenly interested person, with

a ravenous longing for food and a cheery mental attitude toward everything. The changes in this respect appear no greater when the red blood count approaches 5,000,000 per c.mm. than when the liver or extracts produce their initial effects during the first few days.

Hunter[5] considered a seasonal periodicity and indicated July, August and September as months of incidence or recurrence; February, March, April, May and June as months of remissions; October, November, December and January as months in which the disease advanced. In Michigan and the surrounding states there appeared to be equal incidence of relapses in all months, with a slight increase in March (spring).

TABLE II.—MONTHS IN WHICH RELAPSES BEGAN.

	Per cent.		Per cent.		Per cent.
January	9.7	May	7.3	September	6.7
February	5.7	June	7.6	October	9.7
March	11.3	July	8.6	November	8.0
April	6.7	August	9.0	December	9.7

Summary and Conclusions. 1. In pernicious anemia some of the symptoms of a relapse may occur even though a complete blood remission is maintained with liver treatment.

2. "Abortive relapses" are indicated by loss of appetite, exacerbation of symptoms, or the appearance of new symptoms, when the blood is normal or shows no corresponding change.

3. Liver therapy is often discontinued because of the loss of appetite (gastrointestinal or nervous relapse) and a hemopoietic relapse follows.

4. If the liver therapy is maintained the "abortive relapse" may pass into a remission.

5. Relapses may occur in the part of one or more systems without a corresponding involvement of other systems. (Blood, nervous system, gastrointestinal system, bone-joint system, muscular system.)

6. There is a tendency for relapses to recur in similar seasons of the year (about 50 per cent) and this is also true of the "abortive relapses."

7. The incidence of onset or relapse appears about equally distributed through the year.

BIBLIOGRAPHY.

1. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. Am. Med. Assn., 1927, **89**, 759.

2. Minot, G. R.: The Treatment of Pernicious Anemia with Liver or an Effective Fraction of Liver, Trans. Coll. Phys., Philadelphia, 1927, **49**, 144.

3. Sturgis, C. C., Isaacs, R., and Smith, M.: The Treatment of Pernicious Anemia with a Liver Extract, Ann. Int. Med., 1928, **1**, 983.

4. Christian, H. A.: Discussion of Paper on Limitations of Liver Treatment in Pernicious Anemia, J. Am. Med. Assn., 1928, **90**, 2061.

5. Hunter, W.: The Nervous and Mental Disorders of Severe Anemias in Relation to their Infective Lesions and Blood Changes, Proc. Roy. Soc. Med., London, 1922, **16**, 1.

HEMORRHAGES FROM LACERATIONS OF THE CARDIAC ORIFICE OF THE STOMACH DUE TO VOMITING.

By G. Kenneth Mallory, M.D.,
ASSISTANT IN PATHOLOGY, BOSTON CITY HOSPITAL,
AND
Soma Weiss, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Department of Pathology, The Thorndike Memorial Laboratory, and the Fourth Medical Service of the Boston City Hospital; and from the Department of Medicine, Harvard Medical School, Boston, Mass.)

During the past five years we have observed 15 patients who, after a long an intense alcoholic debauch, developed massive gastric hemorrhage with hematemesis. The loss of blood was so great in some of these cases that the patients entered the hospital in circulatory collapse. The characteristic history obtained revealed that after heavy drinking for days or weeks, they experienced persistent nausea, retching and vomiting. Some of the patients had had similar experiences in the past.

The past history and clinical behavior of the patients failed to reveal the source of the hemorrhage. Laboratory tests and careful Roentgen ray studies, undertaken after the bleeding had ceased, were also negative.

The diagnosis of peptic ulcer in the presence of negative findings was not probable. It was obvious that such massive hemorrhages could not be explained by the "alcoholic gastritis." Cirrhosis of the liver was therefore suspected, and although no direct or indirect evidence was obtained for the presence of this disease, it was *assumed* that the source of hemorrhage was a ruptured varix of the esophagus or stomach.

The fact that none of the 15 patients observed showed evidence of cirrhosis of the liver, although 3 of them had had several attacks of hematemesis following alcoholic intoxication, from two to ten years before death, gave rise to the suspicion that the source of bleeding was due to other causes than varices or cirrhosis of the liver. This suspicion was confirmed by the postmortem study of 4 cases, which exhibited strikingly identical lesions at the cardiac opening of the stomach. These consisted of from 2 to 4 definite fissure-like lesions of the mucosa, characteristically arranged around the circumference of the cardiac opening, along the longitudinal axis of the esophagus. The size of the lesions varied from 3 to 20 mm. in length, and from 2 to 3 mm. in width. The edges were raised and slightly thickened, but not indurated. Slight undermining of the edges was occasionally present. In 3 of the cases the lesions were limited entirely

to the stomach, extending almost to the border of the esophagus. In the fourth case the upper quarter of the ulcerations extended into the esophagus. In one of the patients with persistent vomiting no hemorrhage was present at autopsy, but the lesions were identical with those observed in the other 3 patients.

On microscopic section, the lesions were found to be ulcerations of the mucosa, extending as deep as the muscularis. The floor of the ulcers was composed of fresh fibrin and an exudate of polymorphonuclear leukocytes. In some of the sections definitely ruptured arterioles were observed; in others numerous small veins were found in close proximity to the ulcers. Chronic fibrous-tissue reactions were not observed.

Below are presented abstracts of the clinical picture of one of the 11 patients who recovered, and short summaries of the clinical aspects and postmortem findings on 4 patients.

Report of Cases and the Significance of the Observations. CASE I.—J. J., a male, white, American real estate dealer, aged fifty-six years, was brought to the hospital because of severe gastric hemorrhage.

For the past twelve years he had had what he called "nervous indigestion." During this time he had marked heartburn and some gnawing pain in the epigastrium. He thought that this occurred one to two hours after meals, but was much worse in the morning before breakfast. At such time he could get relief by inducing vomiting. Bicarbonate of soda also gave him some relief. He had never had a previous hematemesis and had never noticed bloody or tarry stools. There had been no marked loss of weight.

Alcohol always upset his stomach severely and caused him to vomit excessively. He did not drink every day but at different intervals would go off on a spree and drink heavily for several days or a week. After this, digestive symptoms were much worse. His friends seemed to think that his alcoholic indulgence was a little more constant than he would admit. He admitted drinking heavily for the two weeks preceding entrance to the hospital, averaging from a pint to a quart of whisky daily. Eleven days before entrance he had vomited up some blood but in spite of this he continued to drink. He stated that "about an hour before admission he had had a hematemesis of two quarts of blood." Following this he felt very weak and dizzy. He then apparently lost consciousness for a brief period of time but remembers being brought to the hospital.

Physical examination on entrance showed a well-developed and fairly well-nourished middle-aged man. He was rather garrulous and incoherent. There was a strongly detectable alcoholic odor to the breath. The skin and mucous membranes were rather pale but the patient was distinctly not in a condition of shock. The pulse rate was 100, the systolic blood pressure was 130 mm. of Hg., the diastolic 90 mm. On entrance, the red blood-cell count was 3,170,000 per c.mm., the hemoglobin 60 per cent. By the next day the red blood cells had decreased to 2,720,000 per c.mm., and the hemoglobin to 50 per cent. Physical examination was otherwise essentially negative except that the patient showed slightly generalized arteriosclerosis. There were no signs to suggest cirrhosis of the liver or malignancy.

Fluids were restricted and he was given morphia. No further hematemesis occurred. The stools for three days after admission were tarry, but from then on gradually returned to normal. He was started on a Sippy diet two days after admission.

The patient remained in the hospital three and a half weeks. During his stay he had no vomiting or epigastric distress. Three gastric analyses were done. The first two showed an absence of free hydrochloric acid, but in the third it was normal. Before discharge the red blood cell count had returned to 4,500,000 per c.mm., the hemoglobin to 70 per cent. A Roentgen ray examination of the gastrointestinal tract was made a few days before his discharge. It was reported negative except for a slight diaphragmatic hernia.

DISCHARGE DIAGNOSES. Alcoholic gastritis. Alcoholism, chronic and acute. Generalized arteriosclerosis. Diaphragmatic hernia.

CASE II.—T. K., a male, single, white, longshoreman, aged thirty-five years, during one and a half years had been in the hospital on three different occasions about six months apart because of hematemesis. He first vomited blood ten years ago and had had in all six such experiences. Hematemesis always followed drinking some form of alcohol excessively over a period of from three to four days, and it occurred in the course of subsequent vomiting. No gastrointestinal symptoms had been present except when the patient was drinking. Roentgen ray examination of the gastrointestinal tract two weeks before death was recorded negative. His last hematemesis began about two days before death.

Physical examination the day before death showed that the patient was in a condition of collapse. The liver was palpable 3 cm. below costal margin Otherwise the examination was essentially negative. The heart sounds were rapid and the pulse feeble. In spite of morphia the patient continued to vomit blood and died about twenty-four hours after entry.

Autopsy. (Two hours postmortem.) The body was that of a well-developed, well-nourished, middle-aged white man.

The surfaces of the peritoneal cavity were smooth and glistening. No free fluid was found. The liver edge was 0.5 cm. below the xyphoid and at the costal margin in the midclavicular line.

Pleural and pericardial cavities were negative, and the heart, lungs and spleen essentially normal.

The gastrointestinal tract showed as follows: On opening the cardia of the stomach five narrow fissure-like ulcerations were found distributed around the circumference of the cardia, their upper ends extending into the esophagus. The lesions varied from 10 to 25 mm. in length and 1 to 2 mm. in breadth. They penetrated to the submucosa. The edges were slightly elevated. No bleeding point could be made out. The stomach was empty but the intestines were filled with tarry-black partially-digested blood. No other ulcerations were present and there were no esophageal varices. On microscopic examination these fissures were found to extend down deeply into the submucosa. The floor of the ulcer was covered by an exudation of fibrin and polymorphonuclear leukocytes.

The pancreas was normal, as were the kidneys, adrenals, bladder, aorta and brain.

The liver weighed 1760 gms. Its capsule was smooth. The liver substance was firm and rather reddish-yellow in color. Microscopic examination showed numerous large and small vacuoles in liver cells but no cirrhosis.

Anatomic Diagnosis. Ulcerations of cardiac end of stomach with hemorrhage.

CASE III.—J. M., male, white, aged thirty-one years, was admitted at 3 A.M. vomiting blood. He had been sick three days at home with nausea, vomiting and epigastric distress. His relatives had noticed that he was very nervous and shaky. At 3 P.M. on the day of admission he began to

FIG. 1.—Portion of esophagus and cardia of stomach from patient J. F. (Case IV). Just below junction of esophagus and stomach there are two slit-like ulcerations whose axis is the same as that of the esophagus. The two more superficial oval ulcerations at the lower end of right-hand laceration are probably postmortem changes as microscopic examination showed no cellular reaction or fibrin.

FIG. 2.—Microscopic cross section of ulcer on left side of specimen shown in Fig. 1. There is normal stomach mucosa on both sides of ulcer. The edges are elevated. The floor of the ulcer consists of exudate composed of fibrin and polymorphonuclear leukocytes. An arteriole cut more or less longitudinally can be seen just below the ulceration.

UNIV. OF MICH.

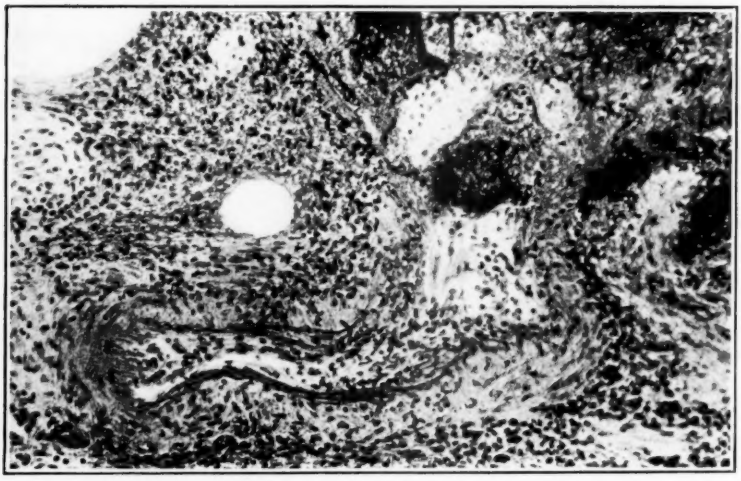


FIG. 3.—Arteriole seen in Fig. 2 but taken from another section. Lumen of vessel contains numerous polymorphonuclear leukocytes. At the uppermost portion of the arteriole the wall has ruptured and hemorrhage occurred. The opening has been filled with a plug of fibrin. *Upper front of picture is the floor of ulceration.* Exudation of fibrin and polymorphonuclear leukocytes can be seen.

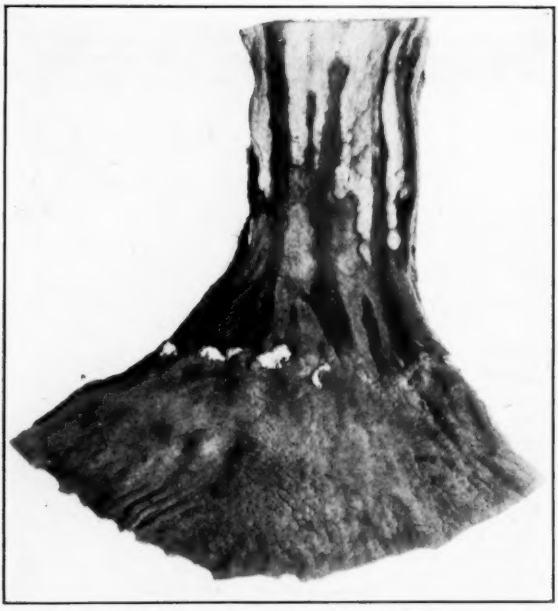


FIG. 4.—Portion of esophagus and cardia of stomach from patient E. F. (Case V). Several fissure-like longitudinal ulcerations can be seen in the first portion of the esophagus. Two are deep, the others rather superficial. There has been complete desquamation of stratified epithelium of the stomach for several centimeters above the juncture of esophagus and stomach.

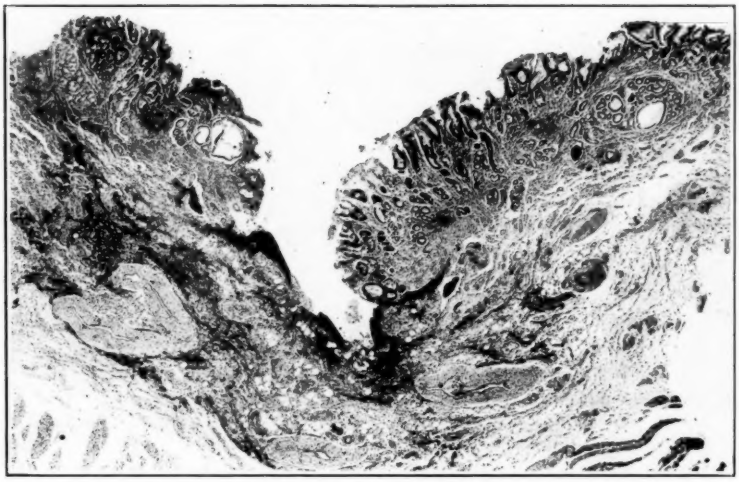


FIG. 5.—Cross section of one of the ulcerations from Case II from the lower end of the lesion. Normal mucosa of stomach is present on either side of ulceration. Fissure is narrow and extends down into the submucosa. The floor is composed of fibrin and polymorphonuclear leukocytes.

FIG. 6.—Similar to Fig. 5 but taken through the esophageal portion of ulceration. Fibrin and leukocytes can be seen to extend laterally from ulcer into the submucosa.

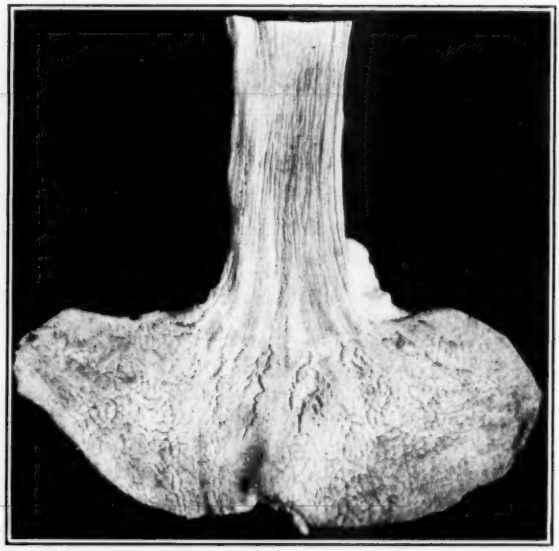


FIG. 7.—Normal esophagus and stomach removed from a child, aged thirteen years, within two hours of death. Numerous rather superficial longitudinal lacerations of the cardia are seen which were produced experimentally by pressure on the stomach after it had been slightly distended with water.

vomit blood profusely and continued to do so until late in the afternoon. The patient's past history was obtained from friends. It revealed that he was a confirmed alcoholic and had been drinking excessively during the past three years.

Physical examination showed a well-nourished, well-developed white man, in a condition of shock. The heart sounds were rapid and feeble, the pulse was of poor quality. There were a few moist râles at both lung bases. Examination was otherwise negative.

The patient continued to vomit small quantities of blood for several hours after admission. The red blood-cell count was 5,690,000 per c.mm., the hemoglobin 60 per cent. When the vomiting ceased the patient's condition did not improve. The pulse rate continued to rise and three days after admission the patient died.

Clinical Discharge Diagnoses. Question of cirrhosis of the liver with ruptured esophageal varix, or bleeding gastric ulcer.

Autopsy. The body was that of a well-nourished, well-developed young white man.

Peritoneal cavity: The subcutaneous fat was 3 cm. in thickness. No free fluid was observed. The liver edge was 3 cm. above xyphoid and 3 cm. above costal margin; it was of normal appearance. The diaphragm lay at the fourth rib on the right and fifth space on the left.

Pleural cavities: A few fibrous adhesions in left cavity were present.

Pericardial cavity was negative. Heart was normal.

Lungs: The right lung showed nodules of consolidation throughout, and the left showed a similar condition at the base.

The liver was large, flabby, opaque, yellow-red, the surface was smooth. On section markings were indistinct.

Spleen, pancreas, kidneys, adrenals, bladder were normal.

Stomach: At the cardia there were three folds which were definitely associated with ulcerative lesions. The edges were slightly thickened and rose above the ulcers. These were almost linear, the longest measuring 15 mm. in length and 3 mm. in greatest breadth. No diffuse bleeding observed. There was a submucous hemorrhage in the cardia and in the submucosa of the esophagus.

Anatomic Diagnoses. Multiple ulcerative lesions of the cardia. Gastric hemorrhage. Terminal bronchopneumonia. Acute dilatation of the right chambers of the heart. Acute passive hyperemia (universal).

CASE IV.—J. F., married, white, male, laborer, aged fifty-six years, was brought to the hospital irrational and mildly delirious. His brother reported that the patient had been a chronic alcoholic for twenty years. Ten years ago he vomited several pints of blood. This recurred about five years ago. Since his last hemorrhage patient had had occasional attacks of epigastric pain associated with nausea and vomiting, which was not related to meals. One week before admission, after a month of excessive drinking, he vomited blood on four occasions. The total amount of this was estimated as about 1½ quarts. Three days before admission he became very restless and irrational.

Physical examination showed a fairly well-developed but poorly nourished middle-aged white man. The conjunctivæ were pale. The pupils were regular and reacted to light and distance. The heart was slightly enlarged, the pulse weak and thready. The abdomen was slightly tender over the epigastrium. The liver dullness appeared diminished by percussion. There was slight twitching of the arms and legs, suggestive of beginning delirium tremens. The systolic blood pressure was 105 mm. of Hg, the diastolic 60 mm. The heart sounds became more rapid and fainter. The patient died within twenty-four hours of admission.

Autopsy. (Twelve hours postmortem.) The body was that of a well-developed, well-nourished middle-aged white man.

Peritoneal cavity: Surfaces were smooth and glistening. No free fluid observed. Liver edge was at xyphoid and 2 cm. above costal margin. The diaphragm lay at the fifth rib on both sides.

The heart showed generalized enlargement with dilatation of the right side was noted.

The lungs were negative except for congestion of bases.

The liver was slightly increased in size, the surface smooth and an opaque yellow-red in color, the markings indistinct.

Gastrointestinal tract: Esophagus was negative. The cardia showed two narrow elongated slits in the mucous membrane, measuring 15 mm. by 3 mm. The edges were elevated but not indurated. In the floor of one of these, there appeared to be a ruptured arteriole. Microscopic examination showed this to be the case, and also that the floor of the ulcer was made up of fibrin, red blood cells, and polymorphonuclear leukocytes. The stomach was free from blood but the colon contained a large amount of brown-black pastelike material.

Spleen, pancreas, kidneys, adrenals, bladder were essentially normal.

Brain showed marked edema of the piaärachnoid.

Anatomic Diagnoses. Ulcers of the cardiac end of the stomach. Hypertrophy of heart. Minor arteriosclerosis of aorta and coronaries. Acute dilatation of the right heart. Universal acute passive hyperemia. Fatty metamorphosis of liver, kidneys, and heart muscle.

CASE V.—E. G., white, male, American, aged sixty-one years, entered the hospital because of pain in abdomen and constant belching of gas. When at home he never indulged in alcohol, but every two to three months he would drink heavily for three or four days. He had done this for about ten years. For twenty years he had been troubled by belching after eating greasy food. He never had colic or abdominal distress after meals, except after alcoholic excess. For about ten years he had been subject to "dry heaves" after such occasions. This would pass off or be relieved by another drink of liquor. There would be no hematemesis or melena.

One week before entrance, after drinking excessively for several days, he was awakened by sharp abdominal pain which persisted more or less until admission to the hospital. It was located to the left and above the umbilicus and radiated only while belching to the xyphoid. During this time the patient had been unable to hold anything on his stomach, vomiting about two minutes after food was swallowed.

Physical examination showed an emaciated and jaundiced man. Slight dullness was present at the right lung base with diminished breath sounds. The abdomen showed so much tenderness and spasm that palpation was difficult. In the epigastrium a mass was felt by some physicians. The liver edge was palpable at about the level of the umbilicus. There was marked arteriosclerosis.

The urine contained a trace of albumin and numerous brown granular casts. The red blood-cell count was 4,340,000 per c.mm. The hemoglobin was 80 per cent. The icteric index was 70. The van den Bergh test showed a delayed direct and an indirect reaction.

On entrance, the patient did not seem in a serious condition, but four days afterward his color suddenly changed to pale red, his pulse became weak, and he died rather suddenly that night.

Clinical Diagnoses. Toxic hepatitis. Carcinoma of head of pancreas. Acute pericarditis. Cholelithiasis and cholecystitis.

Autopsy. (Seven hours postmortem.) The skin and mucous membranes were jaundiced.

Peritoneal cavity contained 200 cc. of thin, bright yellow fluid. The liver edge was 6 cm. below the xyphoid and 2 cm. below the costal margin.

Pleural cavities: About 75 cc. of yellow fluid and fibrin present.

The heart was essentially negative.

The lungs showed bronchopneumonia at right base.

Spleen was negative.

Gastrointestinal: Esophagus showed loss of stratified epithelium for about 2 cm. above cardia of stomach. At the juncture of the esophagus and stomach were several fissure-like longitudinal ulcers. Two of these were deep and penetrated to the muscularis. They measured about 10 mm. in length and 2 mm. in thickness. Microscopic section showed the floor of the lesions to be composed of fresh granulation tissue. There was no blood in the stomach or elsewhere in the gastrointestinal tract.

Pancreas was normal.

Liver: Weight 2100 gm. Moderately enlarged. Normal in shape. Capsule thin over a finely-mottled yellow-brown and red surface. Surface very minutely granular in region of gall bladder and near edges of left lobe. Gall bladder and ducts negative.

Kidneys weighed 620 gm. Edge everted on section. Cortex measured 8 mm. Cut surface is gray-red in color.

Adrenals, bladder, genital organs were essentially normal.

Anatomic Diagnoses. Acute toxic hepatitis. Bronchopneumonia. Acute nephritis. Ulcerative lesions at the cardiac end of the stomach.

Discussion. The identical syndrome presented by these patients suggested that the responsible factor must be either *alcohol, or vomiting* or both. That the vomiting, rather than alcohol, played the more important rôle, is supported by the case of an additional patient with pernicious vomiting of pregnancy. In this patient, at autopsy, there was one laceration at the cardiac opening identical with those described above.

Consideration of bodily changes that occur with vomiting also supports the conception that the vomiting is an etiological agent in the production of hematemesis. Vomiting is a complex reflex act composed of a number of highly coördinated bodily changes.[1] During the stage of nausea the pylorus closes and simultaneously the cardia and esophagus dilate. Counter peristalsis then gradually carries the gastric contents into the cardia and esophagus, and at the onset of retching the relaxed diaphragm assumes a deep inspiratory position. With the sudden convulsive increase of intraäbdominal and intrathoracic pressure, the gastric contents are then ejected. After repeated attacks of vomiting at short intervals fatigue of the vomiting center sets in and[2] this coördination often becomes disturbed, and simultaneously with the convulsive retching movements the esophagus and diaphragm fail to relax. Thus the gastric contents are thrust with great force against the cardiac opening.

In addition to these pressure changes it may be of etiologic significance that during nausea and vomiting, with closure of the pylorus, the gastric juice accumulates in large quantities in the stomach and is carried by the counter peristalsis toward the relaxed cardia and esophagus. The mucosa over this area may be less

resistant to the *digestive action of the gastric juice* and may consequently become damaged or corroded, especially if other factors such as alcohol and pressure disturbances act synergistically.

In order to ascertain whether such mechanical factors as outlined may play a rôle in the causation of ulcerative lesions of the cardiac opening, we have undertaken to determine *experimentally on the human cadaver* which portion of the mucosa is most sensitive to pressure changes during retching. Two normal stomachs with the esophagus and duodenum attached were removed within two hours of death. The pylorus was tied, and the stomach partially filled with water. Then while putting slight pressure on the esophagus, at about the level at which it passes through the diaphragm, the contents of the stomach were forced into the cardia by squeezing the pylorus. When the condition present during retching is thus imitated, one observes that because of the peculiar shape of the cardia, the narrow cardiac opening greatly dilates. On opening the cardia and the esophagus numerous longitudinal lacerations or tears similar in location and distribution to the lesions found in the cases described were found. The rest of the mucosa is normal. It is highly *plausible,* that in patients reported with persistent vomiting of one or more days' duration, similar pressure conditions may be present.

Ulcerative lesions of the mucosa of the cardiac opening of the stomach, although of rare occurrence as compared with similar lesions of the pylorus, occur nevertheless more often than is recognized. The diagnosis is rendered difficult because the lesions are likely to give less prominent symptoms than ulcers of the pylorus, and Roentgen ray observations, unless performed carefully and with skillful technique, are less helpful than in pyloric lesions. The esophagoscope is the most valuable aid in establishing the diagnosis; and with the recent more widespread use of this instrument, ulcers of the lower portion of the esophagus are more often recognized. Recently, the clinical significance of peptic ulcers of the lower portion of the esophagus is becoming more fully appreciated.[3,4]

Excluding ulcerative lesions of the cardiac opening of the stomach, due to a primary condition, such as new growth, infection, corrosive poison, or developmental abnormality, the most important and frequent lesions are peptic and simple ulcers of unknown etiology. Peptic ulcers of the lower portion of the esophagus and cardia were recognized as early as 1839, by Albers.[5] The existence of the condition was nevertheless doubted until Quincke[6] in 1879 established the entity. Since his description over 100 cases have been reported, but only a small number of these have been proved by autopsy and histologic studies. The structural pathology of the peptic ulcers of the cardia and esophagus are identical with those of the stomach and duodenum. The etiologic factors of peptic ulcer, wherever located, remain obscure.

While peptic ulcers of the cardiac opening may be symptomless, in a considerable number of patients retrosternal pain, or pain over the upper part of the back, is present. If the pain is increased during deglutition the presence of the condition is even more suggestive. In addition, vomiting and dysphagia due to spasm may occur. It is advisable to suspect a peptic ulcer in every case of "cardiospasm" until proved otherwise. A separation of peptic and acute ulcers of the cardia, without histologic examination, is impossible.

It is characteristic of *acute ulcers* (sometimes called simple ulcers) that *they produce no symptoms until hematemesis* calls attention to their presence. The microscopic structure reveals them to be of recent formation. They consist of a simple loss of mucosa, with occasional damage to the muscularis. An accumulation of fibrin and polymorphonuclear leukocytes takes place, and finally after careful examination a ruptured bloodvessel is detected. Such lesions of the mucosa of the pylorus and the stomach were fully appreciated by such an authority as Rokitansky.[7]

The occurrence of these acute or simple ulcers close to the cardiac opening was described so vividly by Dieulafoy[8] that following his publication clinicians attributed unexplained gastric hemorrhages to "ulceratio simplex," or to "Dieulafoy's ulcerations."[8] In the first of Dieulafoy's patients a sudden fatal hemorrhage occurred from a superficial "exulceration" "of the size of a five-frank piece," located 2 cm. distal from the cardia. In his second patient the unexpected onset manifested itself in severe hematemesis, which recurred, and during surgical exploration he observed an "exulceration" about the size of a "50-centime piece" near the stomach. In the same year Spiegelberg[9] reported a similar instance occurring in a four days' old baby. At autopsy a pea-sized hemorrhagic area in the mucosa was found at the cardia, in the middle of which was a pinhead-sized superficial ulceration. Since these reports a number of similar cases have been described. In "exulceratio simplex" no etiologic factors can be established and it was suggested by investigators that they might be early stages of peptic ulcers.

We do not believe that our cases are comparable to those of peptic ulcers, or acute simple ulcers described by Dieulafoy and others. A feature of our 4 fatal cases was the gross appearance of the longitudinal fissure-like tears and ulcerations. Histologic examination proved the recent origin of these lesions. The relatively large number of patients who recover spontaneously suggests a strong tendency to healing. Whether the source of bleeding in patients with recurring attacks after repeated alcoholic excess is due to fresh laceration or to the rerupture of vessels in an old lesion cannot be stated with certainty. It is also possible that the lacerations described may lead later to chronic peptic ulcers in some instances.

The conception expressed above that persistent nausea and vomiting—especially if the normal mechanism of the latter is disturbed—is responsible for the lesions of the cardia, is also sup-

ported by 2 of the 3 patients reported by Quincke.[6] Although Quincke's thesis is often quoted as the first proof of the existence of peptic ulcers of the cardia, an analysis of his case reports reveals that only 1 of his 3 patients suffered from peptic ulcer of the esophagus. The condition of his other 2 patients had corresponded exactly to the condition we report upon here. Both were women who vomited intensely and repeatedly before the occurrence of hemorrhage, and in both the diaphragm was pushed upward, due to ascites and metastatic carcinoma in 1 case, and to a huge ovarian cyst in the other. The coördinated mechanism of vomiting was thus interfered with. The lesions found were slitlike tears of the esophagus, involving the mucosa and the muscularis near the cardia. Quincke considered the possibility of vomiting as a cause for the damage, but he discarded this explanation because he had not observed such lesions in other conditions associated with persistent vomiting. It is self-evident that the coördinated changes occurring during vomiting were severely disturbed in these patients, and the condition can be explained by our conception.

In addition to the vomiting, the rôle of alcohol as a predisposing factor cannot be denied. Concentrated ethyl alcohol is a local irritant and an astringent causing temporary or permanent damage to superficial structures. Its rôle in precipitating peptic ulcers was advocated by French clinicians of the nineteenth century.[10,11] The damage to the mucosa of the cardia, where alcohol arrives undiluted from the form in which it is taken, must be greater than on the mucosa of the stomach.

The fact that many patients with most severe and persistent vomiting do not develop gastric hemorrhage does not invalidate our conception of the mechanism of the lesions described. It is seldom that a single etiologic factor precipitates disease. The combined presence of several conditions, some of which are but vaguely recognized, creates pathology in most instances. Persistent retching and vomiting with pressure changes in the stomach, and with the digestive effect of the gastric juice on the mucosa of the cardia, which is probably weakened by the previous damage of alcohol, are the most important causes of the described lacerations and subsequent ulcerations of the cardiac opening of the stomach. The presence of bloodvessels in the lacerated area further determines the severity of the hemorrhage.

Conclusions. 1. Severe, occasionally fatal, gastric hemorrhage with hematemesis may occur after periodic alcoholic debauches.

2. Acute lacerations with ulcerations at the cardiac opening of the stomach were the sources of such fatal gastric hemorrhages in three patients here described.

3. Lacerations of the cardiac opening of the stomach leading to massive hemorrhage may also develop in other diseases, for example, pernicious vomiting of pregnancy and malignant neoplasms, if associated with persistent nausea, retching and vomiting.

4. The responsible etiologic factors producing the described lacerations are: pressure changes in the stomach during a disturbed mechanism of vomiting and continuous regurgitation of gastric juice over the mucosa of the cardia. The local irritant and astringent effect of alcohol as well as the nature of vascularity of the mucosa involved are also predisposing factors.

5. In the presence of obscure gastric hemorrhage, or of hematemesis, lesions at the cardiac opening of the stomach should be thought of and in case surgical interference is undertaken the folds of the cardia should be explored carefully.

NOTE.—We are indebted to Dr. Timothy Leary for his kindness in placing at our disposal some of the autopsy material reported in this paper.

REFERENCES.

1. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, J. Pharmacol. and Exper. Therap., 1923, **22**, 139.
2. Weiss, S., and Hatcher, R. A.: Localization of the Vomiting Center, Proc. Soc. Exper. Biol. and Med., 1922–1923, **20**, 310.
3. Friedenwald, J., Feldman, M., and Zinn, W. F.: Peptic Ulcer of the Esophagus, AM. J. MED. SCI., 1929, **177**, 1.
4. Jackson, Chevalier: Peptic Ulcer of the Esophagus, J. Am. Med. Assn., 1929, **92**, 369.
5. Albers, J. F. H.: Ueber durchbohrende Geschwüre der Speiseröhre und Luftwege, J. d. Chir. u. Augenheilk, 1833, **19**, 1.
6. Quincke, H.: Ulcus œsophagi ex digestione, Arch. f. klin. Med., 1879, **24**, 72.
7. Rokitansky, C.: Lehrbuch der Path. Anat., vol. **2**, 31, Wien, 1849.
8. Dieulafoy, G.: Exulceratio simplex, l'intervention chirurgicale dans les hématemèses foudroyantes consecutives à l'exulceration simple de l'estomac, Bull. de l'Acad. de méd. Paris, 1898, **39–40**, 49.
9. Spiegelberg, H.: Ein Fall von Melæna Neonatorum mit aussergewöhnlichen Sitze der Blutungsquelle, Prag. med. Wchnschr., 1898, **23**, 61.
10. Lancereau, É.: Atlas anatomie path., texte p. 2, plates I and II, Paris, 1871.
11. De La Tourette, G.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1894, 3d série, **11**, 393.

THE PATHOGENICITY OF YEASTLIKE FUNGI ISOLATED FROM THE HUMAN GASTROINTESTINAL TRACT.

BY ROBERT N. NYE, M.D.,

ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL AND INSTRUCTOR DEPARTMENT OF BACTERIOLOGY, HARVARD MEDICAL SCHOOL,

LEON G. ZERFAS, M.D.,

RESIDENT, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

AND

M. AGNES CORNWELL, A.B.,

LABORATORY ASSISTANT, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Boston City Hospital.)

A LARGE number of yeastlike fungi, which were obtained from the gastrointestinal tracts of normal individuals and of others suffering from various diseases, have been described in a previous paper.[1]

The work reported herein concerns experiments carried out to determine the pathogenicity, for rabbits and guinea pigs, of representative strains of this group of fungi.

The majority of recent work along such lines has been done with strains of *Monilia psilosis*. Ashford[2,3] was able to produce systemic mycosis by intravenous injection into rabbits and guinea pigs of strains isolated from the stools of cases of sprue. The virulence could be enhanced by repeated passage through susceptible animals. Smith[4] obtained somewhat similar results; intravenous injection of monilias from sprue cases, except in very small doses, regularly resulted in septicemia and death of the animal. Moniliasis of the gastrointestinal tract could be produced in guinea pigs by intraperitoneal injection or by introduction through a catheter directly into the stomach. A few of Smith's animals, at autopsy, showed lesions of the gastrointestinal tract. On a diet temporarily deficient in vitamin C, only 2 out of 12 guinea pigs survived. Of the 10, 2 died of septicemia, and the other 8 showed striking and uniform lesions of the tongue, ileum and colon. Intravenous injection into rabbits, on the other hand, of relatively large doses of *Monilia albicans*, obtained from 2 cases of thrush, failed to cause death, although a septicemia with liver lesions could occasionally be demonstrated. Dold,[5] however, failed to attach any significance to the results of parenteral injections in animals as a means of differentiating between the monilias obtained from cases of sprue and those from other sources.

In the literature there are numerous references to single strains of monilias, isolated chiefly from cases of chronic pulmonary or gastrointestinal disease, occasionally from abscesses, and rarely from the blood stream. Many of these produced a fatal septicemia in rabbits on intravenous injection, but any attempt at a comparative biologic classification is impossible. Castellani[6] has isolated a number of different species of monilia from cases of sprue and of diarrhea. Tanner, Lampert and Lampert[7] recovered yeastlike organisms from the throats of 10 per cent of over 1000 normal persons and found that many of these were pathogenic for white mice on intraperitoneal injection.

Considerable work has been reported on feeding experiments with *Monilia psilosis*. Ashford[3] was able to produce stomatitis and diarrhea by feeding strains with enhanced virulence, due to animal passage. Similar lesions were obtained with ordinary strains when the guinea pigs were placed on a vitamin-deficient diet. Smith[4] obtained similar results. Fleisher and Wachowiak[8] fed to rabbits a number of yeastlike organisms isolated from the stools of cases with diarrhea and were able to produce diarrhea and, in some cases, death; occasionally, the fungi were recovered from the blood and from lesions in the internal organs. Wood[9] was able to kill guinea pigs by feeding monilias isolated from cases of pernicious anemia.

The blood of such animals, during life, and the organs, at autopsy, were considered by Wood to show changes comparable to those found in pernicious anemia. No mention was made of the extent of anemia, other than a drop in hemoglobin from 88 to 62 per cent in one instance. He also thought that he found evidences of hemolytic anemia in a rabbit that had received daily intravenous injections of sterile filtrates of dextrose water cultures of such monilias. Browne[10] carried out feeding experiments with rabbits using a strain of *Monilia psilosis* obtained from a typical case of sprue. Three rabbits remained healthy over a period of two months. Of the 6 animals which died, 3 showed a progressive anemia and, at autopsy, marked deposits of blood pigment in various organs. Broun, Jacobson and Garcia[11] and Warthin,[12] using strains from cases of pernicious anemia, have failed to confirm the results of these feeding experiments.

It will be noted that a considerable divergence of opinion exists in regard to the pathogenicity of strains of monilias which are apparently identical. The experiments, herewith reported, were undertaken, primarily, with yeastlike fungi isolated from the stools and gastric contents of cases of pernicious anemia. The macroscopic and microscopic lesions and the symptomatic changes that were observed were compared with those that developed in animals after the injection of similar organisms isolated from cases of disease other than pernicious anemia. The latter included several strains of fungi isolated from "thrush" membranes. All of these strains have been shown[1] to be indistinguishable from representative named strains of *Monilia psilosis*. They have been classified together in the specific group, *Parasaccharomyces A*. Numerous experiments are also reported with representative strains of other specific groups, previously defined.[1]

Experimental. No attempt was made to render the animals more susceptible by placing them on a deficient diet. In all experiments, both rabbits and guinea pigs received their usual rations of oats, cabbage, carrots and hay.

Intravenous Injection. *Method.* All strains were grown in dextrose-peptone water at 37.5° C. for approximately forty-eight hours. One or 2 cc. were removed with a sterile pipette and transferred to a test tube. This tube was shaken vigorously for several minutes in order to break up any clumps of the monilia. The culture was then drawn up to the "0.5" mark in a white blood corpuscle counting pipette and diluted with salt solution. After shaking, a counting chamber was filled and the count made. All distinct buds were considered individual organisms. As a rule, the cultures contained approximately 30,000 cells per c.mm., or 30,000,000 (30×10^6) per cc. The organisms were injected into the ear vein of a rabbit. The standard rabbit weight was taken as 1800 gm., and the amount of culture for the required dose was calculated from the weight of the rabbit and the count of the culture. If the necessary amount of culture was less than 5 cc., this amount was made to a total volume of 5 cc. with sterile salt solution; if greater than 5 cc., the culture was centrifuged, the clear supernatant fluid

discarded and the sediment diluted to 5 cc. with sterile salt solution. All rabbits that died were autopsied and, in those that failed to show the typical multiple abscesses of the kidneys, portions of these organs were fixed and sectioned in order to demonstrate the presence or absence of microscopic lesions.

The first experiments were carried out with a strain of *Parasaccharomyces A*, No. 73, isolated from the stool of a case of pernicious anemia. It was found that 20×10^6 organisms per 1800 gm. body weight would cause death in a rabbit five or six days following injection. Similar amounts heated at 60° C. for thirty minutes or amounts less than 10×10^6 were invariably innocuous. Death was preceded by a considerable period of inactivity, accompanied, in the majority of instances, by muscular twitchings and, occasionally, by convulsions. There was a marked loss of weight in animals that received a fatal dose. The organisms could be recovered from the blood stream within twenty-four hours after injection. Cultures taken four to six days afterward, however, were invariably sterile, even in fatal cases. Red blood corpuscle counts and hemoglobin determinations failed to reveal any anemia. The injections were usually followed by slight to moderate increases of the white blood corpuscles, even in animals receiving sublethal doses. The reticulocytes showed no significant changes. Urinalysis from rabbits receiving sublethal doses showed the presence of small amounts of albumin and a few granular casts which appeared two or three days following injection and persisted for four or five days; the blood nonprotein nitrogen remained within normal limits. In fatal cases, albumin appeared in the urine on the second or third day, with or without the presence of casts. One or two days before death, there was complete anuria, accompanied by a marked increase in the nonprotein nitrogen of the blood.

At autopsy, in fatal cases, the cortices of the kidneys were invariably riddled with myriads of small pale-yellow abscesses. A few lesions were occasionally found in the pyramids. In rabbits, which received an overwhelming dose, similar lesions, though fewer in number, could be demonstrated in the heart muscle, and, rarely, in the lungs, liver and wall of the intestines. Microscopically, abscesses have been found in the brain and pancreas. Occasional abscesses in the kidney cortices could be demonstrated in animals which had received sublethal doses and had been subsequently sacrificed. Such animals, however, failed to show lesions in other organs.

In sections from rabbits killed within a few hours after injection, it has been possible to show that the kidney lesions start from individual fungi lodged in the capillary network surrounding the convoluted tubules and, occasionally, in the capillaries of the glomeruli. The organisms grow out into the surrounding tubules and glomeruli, polymorphonuclear leukocytes appear, the normal kidney structure is destroyed and the typical miliary abscess results.

The lesions in the pyramids are apparently secondary to the presence of exudate in the collecting tubules. Viable fungi can be recovered from the urine. If the lesions are too few to produce sufficient cortical destruction to result in death, they heal with the formation of scar tissue. In animals which were sacrificed ten days to two weeks following injection and which, grossly and microscopically, showed a moderate number of kidney lesions in various stages of healing, it was impossible to demonstrate the organisms in sections stained by the Gram-Weigert method.

Smears and cultures of the kidneys taken at autopsy in fatal cases were invariably positive. Blood cultures, on the other hand, were always negative.

The accompanying tables (Tables I and II) give abbreviated records of animals which are representative of the group as a whole.

The pathogenicity and lethal dose of various strains of *Parasaccharomyces A* and of strains of other specific and generic groups were also determined by intravenous injections in rabbits. These results are briefly summarized in Table III. It will be seen that all strains of *Parasaccharomyces A*, regardless of their source and age, were able to cause death in amounts ranging from 2×10^6 to 100×10^6 organisms per 1800 gm. body weight. The macroscopic and microscopic findings were identical with those described following injection with *Parasaccharomyces A*, No. 73. All of the other groups of parasaccharomycetes and representatives of the two other generic groups, however, were apparently innocuous, even with amounts as large as 100×10^6, with the exception of *Parasaccharomyces B*. It should be remembered that the latter species is morphologically indistinguishable, but culturally somewhat different, from *Parasaccharomyces A*. With this organism death did occur with a 100×10^6 dose and typical lesions were found. In order to determine whether or not nonfatal kidney lesions were present following injection with fungi from this large group of relatively nonpathogenic strains, rabbits were inoculated intravenously with 100×10^6 organisms and sacrificed five days later. All kidneys were grossly negative and abscesses were found microscopically only in the rabbit which received *Parasaccharomyces B*.

All but three of the *Parasaccharomyces A* strains were fatal in numbers ranging from 2×10^6 to 20×10^6 per 1800 gm. body weight. One of these three strains was obtained from Dr. B. K. Ashford (*Monilia psilosis*, No. 34*a*) and another from the late Dr. Edwin J. Wood (*Monilia psilosis*, Si.). Although the date of their isolation is unknown, probably both had been kept on artificial media for at least two or three years. The third strain, No. 73, tested twenty-three months following isolation, had a lethal dose of 100×10^6, although a year previous only 20×10^6 organisms were necessary to cause death. Ashford's strain was also tested following 3 direct rabbit-blood transfers and it was found that the

TABLE I.—ABBREVIATED PROTOCOLS OF RABBITS INJECTED INTRAVENOUSLY WITH VARYING AMOUNTS OF PARASACCHAROMYCES A, NO. 73.

Day following injection.	Rabbit No. 1. 20 x 10^6 organisms per 1800 gm. body weight.				Rabbit No. 2. 20 x 10^6 heat-killed organisms per 1800 gm. body weight.				Rabbit No. 3. 10 x 10^6 organisms per 1800 gm. body weight.				Rabbit No. 4. 5 x 10^6 organisms per 1800 gm. body weight.			
	Weight, gm.	R. B. C. x10^6	Hgb., per cent	W. C. x10^3	Weight, gm.	R. B. C. x10^6	Hgb., per cent	W. C. x10^3	Weight, gm.	R. B. C. x10^6	Hgb., per cent	W. C. x10^3	Weight, gm.	R. B. C. x10^6	Hgb., per cent	W. C. x10^3
	1673	4.2	63	27	1625	5.1	67	6	1721	6.2	65	6	2190	5.1	64	12
1	1555	3.6	56	18	....	...	..	..	1693	6.0	61	11	2092	5.1	57	11
2	....	...	..	..	....	...	..	..	1540	5.8	61	14	2040	4.9	56	15
3	1407	3.8	53	35	1505	5.0	67	8	1407	6.2	72	14	2081	5.2	63	16
4	....	...	..	..	....	...	..	..					....	...	..	..
5					....	...	..	..					1855	...	..	..
6					....	...	..	..	1290	Found dead (*fourth day*)			....	...	..	..
7	1242	Found dead (*fifth day*)			....	...	..	..					1863	...	..	..
8					1535	...	..	..					....	...	..	..
13					....	...	..	..	Marked diarrhea 2 days before death. Autopsy, multiple abscesses in kidneys.				....	...	..	..
14	Autopsy, multiple abscesses in kidneys. Iron reaction negative on pieces of liver and kidney.				1505	...	..	..					....	...	..	..
19					1496	6.1	74	12					1850	...	..	..
					Survived								Survived			

TABLE II.—URINARY AND BLOOD-NITROGEN FINDINGS IN RABBITS FOLLOWING FATAL AND NONFATAL DOSES OF PARASACCHAROMYCES A.

Days before or following injection.	Rabbit No. 9. 10 x 10^6 organisms from 24-hour culture of *Parasaccharomyces A*, No. 73, injected intravenously.							Rabbit No. 10. 20 x 10^6 organisms from 24-hour culture of *Parasaccharomyces A*, No. 73, injected intravenously.						
	Weight, gm.	Urine.					Blood N. P. N., mg. per 100 cc.	Weight, gm.	Urine.					Blood N. P. N., mg. per 100 cc.
		Amount, cc.	Reaction.	Specific gravity.	Albumin.	Sediment.			Amount, cc.	Reaction.	Specific gravity.	Albumin.	Sediment.	
2	2067	320	Alk.	1.008	0	Neg.	36.7	2449	320	Alk.	1.014	0	Neg.	30.7
1	1968	150	Alk.	1.018	0	Neg.	....	2417	410	Alk.	1.010	0	Neg.	.....
	2037	290	Alk.	1.015	0	Neg.	....	2412	470	Alk.	1.012	0	Neg.	.....
1	....	180	Alk.	1.015	0	Neg.	....	....	260	Alk.	1.014	0	Neg.	.....
2	1870	180	Alk.	1.015	S. P. T.	Neg.	....	2202	110	Alk.	1.012	S. P. T.	Neg.	.....
3	1875	100	Alk.	1.022	0	Neg.	....	2145	110	Alk.	1.018	L. T.	Neg.	.....
4	1860	37	Str. alk.	1.025	T.	Occ. gran. cast	40.0	2117	0	...	.....	....	....	131.8
5	1827	115	Str. alk.	1.018	S. P. T.	Occ. gran. cast	....	2045	0	Found dead				
6	1802	300	Alk.	1.017	S. P. T.	Occ. gran. cast	....	Autopsy—generalized multiple abscesses.						
7	1757	55	Alk.	1.025	0	Neg.	....							
8	1818	Survived					41.0							

TABLE III.—SUMMARY OF RESULTS FOLLOWING THE INTRAVENOUS INJECTION INTO RABBITS OF KNOWN DOSES OF VARIOUS YEASTLIKE FUNGI.

Classification of the fungus.	Strain.	Source.	Clinical diagnosis.	Age of culture.	Intravenous dose—x10⁶ organisms per 1800 gm. body weight.						
					1	2	5	10	20	40	100
Parasaccharomyces A	No. 4	Stool	Pernicious anemia	13 mos.	S	..	**D 5**	D 4	D 3		
				24 mos.	D 8	**D 3**	D 7	D 4	D 4		
					S						
Parasaccharomyces A	No. 73	Stool	Pernicious anemia	11 mos.	..	..	..	S	**D 5**	D 7	
					..	..	..	D 5	D 9		
				23 mos.	..	..	..	..	S	S	**D 5**
Parasaccharomyces A	No. 31a	Stool	Typhoid fever	14 mos.	..	..	S	S	**D 7**		
Parasaccharomyces A	No. 39	Stool	Congenital heart disease	14 mos.	..	..	**D 12**	D 5	D 5		
				25 mos.	..	S	**D 8**				
Monilia psilosis	No. 34a	Stool	Sprue	?	..	..	..	..	S	S	**D 7**
				3 rabbit transfers	..	..	..	S	S	**D 8**	
Monilia psilosis	Si.	Stool	? Sprue	?	..	..	..	S	S	**D 7**	D 5
Parasaccharomyces A	B–14–16	Throat	Thrush	1 mos.	..	..	..	S	**D 3**		
Parasaccharomyces A	B–26–2541	Throat	Thrush	5 mos.	..	..	S	**D 5**	D 5	D 3	
Parasaccharomyces A	U–26–37	Esophagus	Severe malnutrition (autopsy)	3 mos.	S	..	**D 5**	D 8	D 4		
Parasaccharomyces B	No. 130	Gastric contents	Pernicious anemia	22 mos.	..	..	..	..	..	S	S
					..	..	..	..	..	..	D 15
Parasaccharomyces C	No. 67	Gastric contents	Chronic nephritis	22 mos.	..	..	..	..	..	..	*S*
Parasaccharomyces D	No. 18	Stool	Pernicious anemia	22 mos.	..	..	..	..	S	..	*S*
Parasaccharomyces E	No. 106	Stool	Hysteria	22 mos.	..	..	..	..	S	..	*S*
? Parasaccharomyces I	No. 31b	Stool	Typhoid fever	23 mos.	..	..	..	..	..	S	*S*
Cryptococcus A	No. 16b	Gastric contents	Carcinoma of stomach	24 mos.	..	..	..	..	..	S	*S*
Endomyces A	No. 123	Stool	No disease	21 mos.	..	..	..	..	..	S	*S*

S = survived D = died (number = day following injection) with bold-face type indicating minimal lethal dose.

lethal dose had been reduced from 100 x 10^6 to 40 x 10^6 organisms. These results would seem to indicate that the virulence diminishes with the age of culture. One strain, *Parasaccharomyces A*, No. 4, however, which, incidentally, had the lowest lethal dose, retained its original virulence even after two years on artificial media. Furthermore, the lethal doses of fairly recently isolated "thrush" strains were practically of the same magnitude as those of intestinal strains which had been kept on artificial media for more than a year.

Intraperitoneal Injection. Rabbits were injected intraperitoneally with known amounts of two strains of *Parasaccharomyces A*, No. 4 and No. 73, both isolated from cases of pernicious anemia. With the former, 200 x 10^6 organisms per 1800 gm. body weight, or 100 times the fatal intravenous dose, were required to cause death, which occurred in five days. With the latter, 650 x 10^6 organisms, or 30 times the fatal intravenous dose, caused no apparent ill effects, whereas 500 x 10^6 organisms, injected intraperitoneally two weeks following the first injection, caused death in twenty-four hours. At autopsy the outstanding lesion, in both instances, was a marked fibrinous peritonitis; a few abscesses were found in the kidneys and liver, but they apparently had arisen from subcapsular infection. In spite of the massive doses received, there was no evidence of invasion, with subsequent blood-stream infection. In animals that received sublethal doses there was a steady increase in body weight over a period of two or three weeks and the blood picture remained normal.

A series of 38 guinea pigs, weighing approximately 300 gm. each, was injected intraperitoneally with 250 x 10^6 organisms from four-day dextrose peptone water cultures of 38 different strains. From half of these animals satisfactory stool cultures were obtained prior to injection—8 were negative for yeastlike fungi, 10 yielded organisms similar to *Parasaccharomyces C* and one a strain similar to *Parasaccharomyces A*. The animals were weighed and their stools cultured at two-, four- and nine-week intervals. Only 4 of the guinea pigs showed organisms in the stools similar to those injected—3 of these showed no ill effects from the injections and were discarded at the end of two months; the other, which died after four and a half weeks, showed no lesions, at autopsy, which could be attributed to the fungi. Of the 38 guinea pigs, 24 died after periods ranging from four days to nine and a half weeks—unfortunately all of the guinea pigs were, at that time, going through a serious epidemic of pneumonia. Of these 24 animals, 9 showed, at autopsy, unilateral or bilateral pneumonia, 14 no demonstrable lethal lesions, and one a purulent peritonitis. The latter animal died four days after the injection of *Parasaccharomyces A*, No. 4, which strain, it will be recalled, was found to be relatively virulent for rabbits. In this one instance, death was apparently due to the fungi. Cultures taken of the hearts' blood of the autopsied animals were consistently negative.

Tiny subcutaneous abscesses at the site of injection and localized peritonitis, particularly in the neighborhood of the pancreas, with or without small abscesses, were frequently observed and cultures from such abscesses usually yielded yeastlike fungi. Sections of the organs examined microscopically showed no evidence of a generalized infection and Gram-Weigert stained sections of the pneumonic lungs were negative for fungi.

Several guinea pigs were injected intraperitoneally with increasing amounts, up to 5 cc., of four- and seven-day Berkefeld filtrates of *Parasaccharomyces A*, No. 73, cultures in dextrose peptone water. No ill effects were noted.

Intradermal Injection. Rabbits and guinea pigs were injected intradermally with four- and seven-day Berkefeld filtrates of *Parasaccharomyces A*, No. 73, cultures in dextrose peptone water. The skin reactions were consistently negative.

Feeding. Three guinea pigs were fed cultures of three different strains of *Parasaccharomyces A* (*Monilia psilosis*, No. 6 and *Parasaccharomyces A*, No. 73 and No. 131) for a period of one month. Three cubic centimeters of a twenty-four-hour dextrose peptone water culture were fed daily by mixing with chopped cabbage and carrots. As will be seen from Table IV, the animals gained steadily in weight and the blood pictures remained essentially normal. They were killed at the end of a month. There were no gross lesions and portions of the livers, kidneys and spleens failed to give any test for hemosiderin. The organisms were recovered on culture from the intestinal tract.

Discussion. In an earlier paper[1] it was emphasized that the majority of yeastlike fungi isolated in appreciable numbers from human stools and gastric contents, particularly the former, are morphologically and culturally identical. These organisms were all included in the specific group, *Parasaccharomyces A*. In this group, also, were placed various-named species of monilia and yeastlike organisms obtained from typical "thrush" membranes. This specific identity is further substantiated by the pathogenicity of various strains, regardless of their source, when injected intravenously, in fairly large numbers, in rabbits. The difference, as regards pathogenicity, between *Parasaccharomyces A* and the other groups of parasaccharomycetes is striking. Only one other group, *Parasaccharomyces B*, was able to produce lesions, even in relatively large amounts. This group morphologically, and, in certain respects, culturally, is identical to *Parasaccharomyces A*. Representatives of the two other generic groups, cryptococci and endomycetes, were harmless.

These findings would seem to indicate that, in judging whether or not a certain yeastlike fungus is "pathogenic," but little significance can be attached to the fact that it is able to cause death when injected intravenously in a rabbit. Such a strain would probably fall into the large specific group, *Parasaccharomyces A*, but repre-

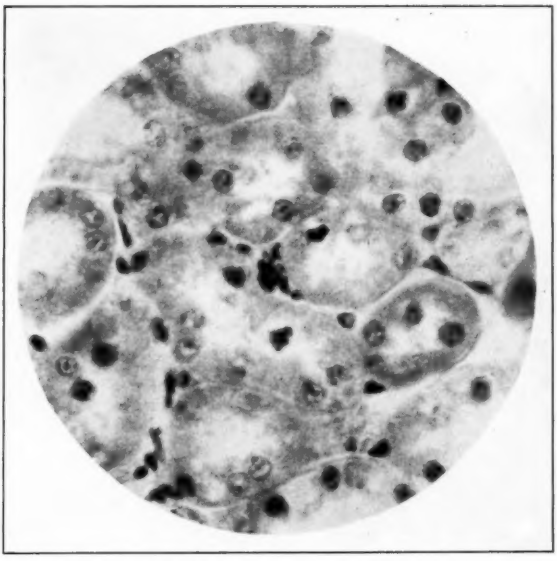


FIG. 1.—Rabbit No. 508, killed five hours after the intravenous injection of 50 x 10^6 *Parasaccharomyces A.* Section of kidney, Gram-Weigert stain. × 1000. In the center of the field is a single organism, located in an intertubular capillary.

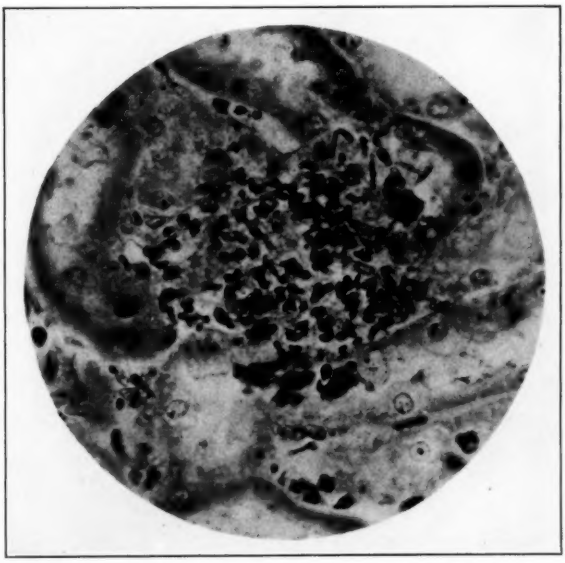


FIG. 2.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of 50 x 10^6 *Parasaccharomyces A.* Section of kidney, eosin and methylene blue stain. × 700. The lesion is more advanced. Several tubules are involved and there is a definite focus of acute inflammation. Numerous elongated forms of the fungus can be seen in the lumen of the convoluted tubule in the upper half of the field.

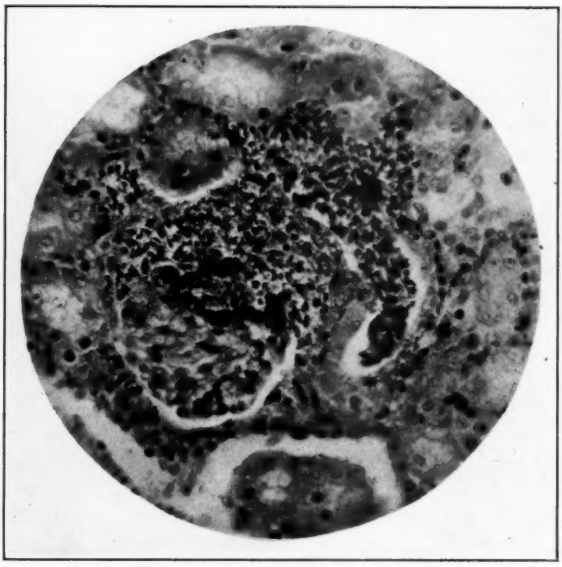


FIG. 3.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of 50 x 10^6 *Parasaccharomyces A*. Section of kidney, eosin and methylene-blue stain. × 500. This lesion involves a glomerulus. The acute inflammatory exudate can be seen in the glomerular tuft and capsule, in the surrounding kidney tissue, and in the lumen of an adjacent convoluted tubule.

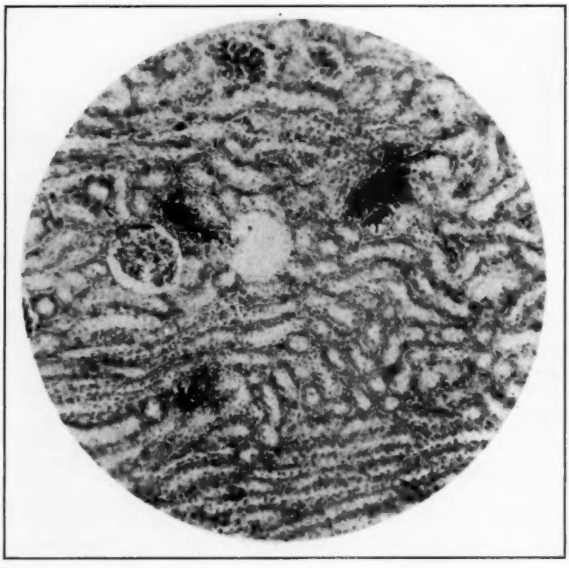


FIG. 4.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of 50 x 10^6 *Parasaccharomyces A*. Section of kidney, Gram-Weigert stain. × 160. A lower magnification showing lesions similar to the two preceding, but stained in such a way as to bring out the colonies of fungi.

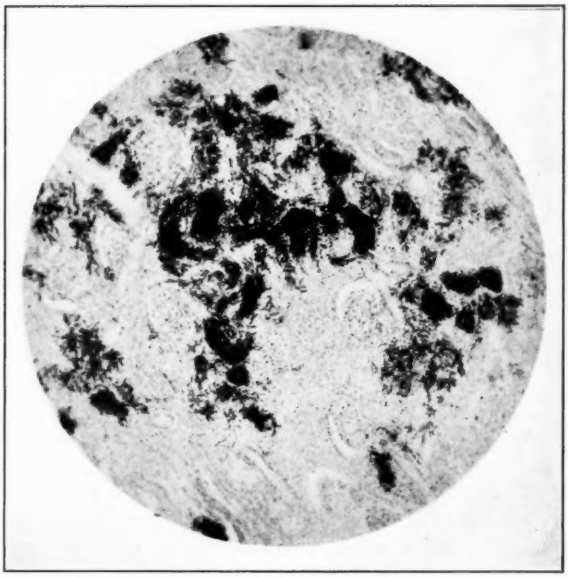


FIG. 5.—Rabbit No. 120, found dead four days after the intravenous injection of 40 x 10^6 *Parasaccharomyces A.* Section of kidney, Gram-Weigert stain. × 125. An atypical reaction, in that there are an enormous number of organisms with very little inflammatory reaction. The large compact masses are contained in the dilated lumina of convoluted tubules.

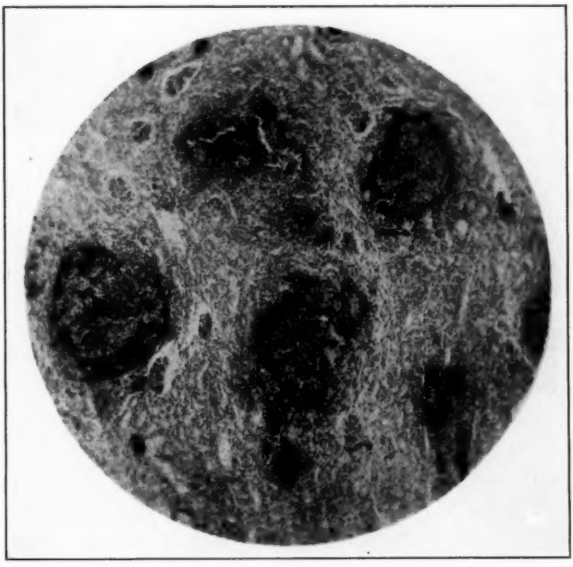


FIG. 6.—Rabbit No. 25–1, found dead five days after the intravenous injection of about 20 x 10^6 *Parasaccharomyces A.* Section of kidney, eosin and methylene-blue stain. × 100. Advanced lesions showing definite abscess formation with extensive destruction of kidney tissue.

TABLE IV.—PROTOCOLS OF GUINEA PIGS THAT RECEIVED DAILY FEEDINGS OF FRESH CULTURES OF DIFFERENT STRAINS OF PARASACCHAROMYCES A.

Days after feeding began.	Guinea pig No. 1. *Parasaccharomyces A*, No. 131.				Guinea pig No. 2. *Parasaccharomyces A*, No. 73.				Guinea pig No. 3. *Monilia psilosis*, No. 6.			
	Wt., gm.	R. B. C. x10⁶	Hgb., per cent.	W. B. C. x10³	Wt., gm.	R. B. C. x10⁶	Hgb., per cent.	W. B. C. x10³	Wt., gm.	R. B. C. x10⁶	Hgb., per cent.	W. B. C. x10³
	380	5.4	74	22	377	5.5	77	13	393	5.9	78	11
1	391	...	..	..	401	...	..	..	386	...	..	..
3	374	5.9	77	20	365	6.2	75	15	374	6.5	83	14
6	400	...	..	..	410	...	..	..	388	...	..	..
11	410	...	..	..	408	...	..	..	384	...	..	..
13	372	...	..	..	376	...	..	..	368	...	..	..
16	407	5.8	65	19	395	5.8	76	17	387	4.8	63	13
20	394	...	..	..	394	...	..	..	384	...	..	..
22	422	...	..	..	415	...	..	..	417	...	..	..
23	...	5.4	72	15	...	5.5	71	17	...	5.9	68	15
24	430	...	..	..	409	...	..	..	432	...	..	..
27	423	...	..	..	419	...	..	..	421	...	..	..
30	447	4.9	63	14	434	5.6	75	15	445	5.2	68	10

All 3 guinea pigs were killed on the thirtieth day. Autopsies, no gross or microscopic lesions, negative tests for hemosiderin on pieces of livers, kidneys and spleens, yeastlike organisms, morphologically and culturally identical with those fed, were recovered in each instance from the intestinal contents.

sentatives of this group have been recovered from the stools and gastric contents in a wide variety of conditions where there was no indication of abnormality in the gastrointestinal tract.

The nonpathogenicity of the other specific and generic groups is in accord with the findings of many other investigators when working with cultures of "wild yeasts." The criterion by virtue of which the term "wild yeast" is applied is somewhat doubtful, but it would seem, in general, that the adjective "wild" is applied to any yeastlike organism which is nonpathogenic to the rabbit on intravenous injection. No hint has been obtained as to the fate of these nonpathogenic strains in the rabbit.

The pathologic findings in the organs, particularly the kidneys, of rabbits that had been sacrificed or had succumbed following the intravenous injection of *Parasaccharomyces A* were extremely interesting. The typical miliary abscesses, except after overwhelming doses, were found almost exclusively in the cortices of the kidneys, in spite of the fact that individual fungi could be demonstrated in the capillaries of the lungs, liver, spleen, and heart muscle an hour after injection. It would seem likely that this particular portion of the kidneys offers a more favorable site for the growth of the fungi, possibly on account of better conditions of hydrogen-ion concentration or of nutrition. From their original location in the intertubular capillaries and, more rarely, those of the glomeruli the organisms proceed to multiply and to invade the contiguous tissue; and, an abscess results. Death, in such cases, would appear to result primarily from extensive kidney damage, for it is preceded by complete anuria, a marked increase in blood nonprotein nitrogen, collapse and, frequently, muscular twitchings and convulsions. When large numbers of the organisms were injected, abscesses were found in other parts of the body. Gastrointestinal lesions were never found except in animals that had received an overwhelming dose and, in such cases, the lesions consisted of abscesses identical with those found in practically every organ of the body. Diarrhea was sometimes present in fatal cases, but was not a consistent finding. The rabbits showed no striking change in the blood picture and the organs at autopsy, failed to give an iron reaction indicative of liberation of abnormal amounts of hemoglobin-derived pigments.

In a series of guinea pigs, that received large intraperitoneal doses, the animals did not die of lesions that could be attributed to fungus infection, with one exception, and this one died very acutely with a marked purulent peritonitis. It is true that the results might have been different, if the animals had been placed on particular diets deficient in one or more vitamins, minerals, or other substances.

Even though it is accepted that *Parasaccharomyces A* is pathogenic for rabbits, it must be acknowledged that the virulence is exceedingly low and that the fatal lesion is quite unusual. A considerable number of organisms must be injected intravenously in order to produce

death. Sublethal doses cause a varying number of abscesses in the kidneys, but these lesions are quickly mastered by local or circulating protective factors and subsequent systemic infection never occurs. Even in fatal cases, fungi were never recovered from the hearts' blood provided a period of two days had elapsed since the last injection. This lack of invasive power is also clearly demonstrated by the observations on rabbits that received intraperitoneal injections. In one instance, 100 times the lethal intravenous dose was required to produce death; and, even then, there was no evidence, macroscopically or microscopically, of blood-stream infection. The pathologic findings, following intravenous injection, seem to be directly proportional to the number of organisms injected. With sublethal and minimal lethal amounts, the lesions were confined, practically entirely, to the kidneys, but, as the dose was increased, more organs were found to be involved.

Guinea pigs fed normal diets containing cultures of *Parasaccharomyces A* failed to show any ill effects. The gain in body weight was progressive and there was no evidence of anemia.

The evidence accumulated in the work reported here and in the previous paper[1] would seem to warrant the conclusions that the yeastlike fungi occur quite commonly in the human gastrointestinal tract and that, with the exception of *Parasaccharomyces A*, they are essentially saprophytic. That this one species is relatively parasitic is evidenced by the fact that it is about the only one to be recovered in appreciable numbers from human stools. If animals are injected with sufficient numbers of a strain of *Parasaccharomyces A*, intravenously or intraperitoneally, or, if, as other investigators have shown, the normal protective agencies are diminished by certain vitamin-deficient diets, lesions result and death ensues. The parallel of the latter condition exists in the human body, for it is a well-known fact that in the one condition, "thrush," in which the etiologic factor is undoubtedly a parasaccharomyces and probably one belonging to the specific group, *Parasaccharomyces A*, a state of lowered resistance in the patient is usually a pre-requisite. Thrush membranes, as stated by Osler,[13] most commonly occur "in enfeebled, emaciated infants with digestive or intestinal troubles" and "in adults in the final stages of fever, in chronic tuberculosis, diabetes, and in cachectic states." There are undoubtedly authentic cases in which death has been due to a generalized infection with these organisms. In such cases, however, there was probably some underlying cause which permitted the invasion and multiplication of the fungus. The same holds true for other common relatively nonpathogenic inhabitants of the gastrointestinal tract—for instance, *Bacillus proteus*.

Conclusions. 1. Yeastlike fungi belonging to the specific group, *Parasaccharomyces A*, regardless of their source, are pathogenic for rabbits following intravenous injection.

2. Representative strains of other specific and generic groups of yeastlike fungi, isolated from the gastrointestinal tract, are non-

pathogenic, at least when injected intravenously in rabbits in large doses.

3. Relatively large doses of *Parasaccharomyces A* are necessary to cause death in rabbits and the invasive power of such organisms, as judged by observations on animals following intraperitoneal injection, is practically nil.

4. Death in rabbits following the intravenous injection of *Parasaccharomyces A* is due, primarily, to extensive renal damage, with a resulting uremia.

5. No gastrointestinal lesions or noteworthy changes in blood picture were observed in guinea pigs fed for a month with fresh cultures of *Parasaccharomyces A* in addition to a normal diet.

6. These facts, together with others previously reported, seem to warrant the conclusions that the yeastlike fungi classified as *Parasaccharomyces A* are relatively common in the human gastrointestinal tract and that their importance in human pathology rests in their possible rôle as infectious agents in conditions of lowered resistance.

REFERENCES.

1. Nye, R. N., Zerfas, L. G., and Cornwell, M. A.: Am. J. Med. Sci., 1928, **175**, 153.
2. Ashford, B. K.: Am. J. Med. Sci., 1915, **150**, 680.
3. Ashford, B. K.: Am. J. Med. Sci., 1916, **151**, 520.
4. Smith, L. W.: J. Am. Med. Assn., 1924, **83**, 1549.
5. Dold, H.: China Med. J., 1917, **31**, 387
6. Castellani, A.: J. Trop. Med. and Hyg., 1914, **17**, 305.
7. Tanner, W., Lampert, E. N., and Lampert, M.: Centralbl. Bakt., Abt. 1, Orig., 1927, **103**, 94.
8. Fleisher, M. S., and Wachowiak, M.: Am. J. Med. Sci., 1924, **168**, 371.
9. Wood, E. J.: Am. J. Med. Sci., 1925, **169**, 28.
10. Browne, D. C.: Proc. Soc. Exper. Biol. and Med., 1927, **24**, 873.
11. Broun, G. O., Jacobson, C., and Garcia, O.: J. Clin. Invest., 1926, **2**, 607.
12. Warthin, A. S.: Ann. Clin. Med., 1927, **5**, 808.
13. Osler, W.: The Principles and Practice of Medicine, New York and London, 1925.

THE CEREBRAL CIRCULATION.

IX. The Relationship of the Cervical Sympathetic Nerves to Cerebral Blood Supply.*

By Stanley Cobb, M.D.,

Professor of Neuropathology, Harvard Medical School, Boston, Mass.

(From the Department of Neuropathology, Harvard Medical School, Boston, Mass.)

For more than thirty years there has been a controversy as to whether or not cerebral vessels are under vasomotor control. This paper is an attempt to indicate briefly the history of the subject and

* Read at the meeting of the Association for Research in Nervous and Mental Disease, New York, December 27, 1928.

to report in a summary way some recent work* from the Department of Neuropathology at the Harvard Medical School.†

The standard textbooks on physiology in English give the impression that the question is settled: that there is no such control, and, in fact, that there are no nerves to the vessels of the brain. For example, Bayliss (1924)[1] states: "As will be seen later, there is no adequate evidence that the cerebral vessels have any vasomotor control; the importance of the brain is such that its circulation is regulated by the whole of the rest of the body, which is caused to accommodate itself, by constrictor and dilator nerves, to the needs of the brain." On the other hand, clinicians have long accepted "cerebral vascular spasm" as the cause of transient hemiplegia, aphasia, migraine and convulsion. For example, we find in "Cecil's Textbook of Medicine" (1927):[2] "There have been reported cases of transitory hemiplegia resulting from *cerebral vascular spasm*. The condition is allied to intermittent claudication of the lower extremities. These 'vascular crises,' as they have been termed by Pal, are particularly common in smokers."

The physiological dogma that the cerebral vessels lack all vasomotor control seems to have its origin in the work of Leonard Hill (1896).[3] Hill's experiments led him to conclude that in every experimental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures, and that there is no evidence for the causation of cerebral anemia by spasm of the cerebral arteries. These sweeping conclusions have been accepted without critical examination by the writers of most textbooks. The work of Weber (1908)[4] does not appear to have been read by many English-speaking physiologists. Experimenting with cats, he found in 75 per cent a decrease in brain volume following stimulation of the cervical sympathetic. He criticized Hill's method because it did not take into account changes in pressure due to an increase in the amount of cerebrospinal fluid, a factor which might well mask the effects of vascular change as determined by Hill. He, therefore, considered Hill's method inadequate and his conclusions false. Weber's work, though excellently done, gives only indirect evidence. The vessels of the brain were not actually seen to change in caliber;

* For a detailed discussion see Lennox and Cobb.[33]

† The individual studies are as follows: Observation and Measurement of Pial Vessels: H. S. Forbes, Arch. Neurol. and Psychiat., 1928, **19**, 751. A Quantitative Study of Cerebral Capillaries: S. Cobb and J. H. Talbott, Trans. Assn. Am. Phys., 1927, **42**, 255. The Vasomotor Control of Cerebral Vessels: H. S. Forbes and H. G. Wolff, Arch. Neurol. and Psychiat., 1928, **19**, 1057. The Action of Hypertonic Solutions—Part I: H. G. Wolff and H. S. Forbes, Arch. Neurol. and Psychiat., 1928, **20**, 73. Observations of the Pial Circulation during Changes in Intracranial Pressure, H. G. Wolfe and H. S. Forbes, Arch. Neurol. and Psychiat., 1928, **20**, 1035. Velocity of Intracranial Blood Flow: H. G. Wolff and H. Blumgart, 1928, Arch. Neurol. and Psychiat, **21**, 795. Changes in Cerebral Capillary Bed following Cervical Sympathectomy: J. H. Talbott, H. G. Wolff and S. Cobb, 1929, Arch. Neurol. and Psychiat. (in press). Quantitative Study of the Capillaries in the Hippocampus: S. Cobb, Arch. Surg., 1929, **18**, 1200.

he argued that they must contract and dilate because brain volume changed and all other variables were controlled.

Müller and Siebeck (1907)[5] carried out experiments which indicated that there was a distinct and fairly rapid increase in the volume of the brain after section of the cervical sympathetic, the systemic blood pressure remaining at a constant level. Hürthle (1889)[6] and others in his time measured the pressure in the circle of Willis. Stimulation of the cervical sympathetic nerves caused an increased arterial pressure synchronous with a drop in jugular venous pressure. For a comprehensive bibliography, the reader is referred to Tigerstedt's *Physiologie des Kreislaufes* (1923)[7] and to the recent paper by Forbes and Wolff (1928).[8]

A series of experiments by Talbott, Wolff and Cobb (1928),[9] that have not yet been published, may be briefly reported here. Ten cats were operated upon under ether anesthesia. In each the left cervical sympathetic nerve was aseptically exposed, cut and approximately 2 cm. removed. An increase in temperature of the ear and a constriction of the pupil on the operated side was accepted as evidence that the cervical sympathetic nerve had been cut. After a lapse of time varying from one hour to six days, the vessels of the head and brain were injected with a 2 per cent aqueous solution of Berlin blue. The injection method is briefly as follows:

After anesthetization with ether the thorax was rapidly opened and the heart and great vessels were exposed. The internal mammary arteries and the abdominal aorta were clamped. The pericardial sac was next opened and an incision was made through the wall of the left ventricle. A cannula was inserted through the incision and carried past the aortic valves into the ascending aorta and ligatured. The injection mass, warmed to body temperature, was then allowed to run in at a constant pressure varying between 220 and 225 mm. of mercury. Ludwig's injection apparatus was used. With this apparatus the injection pressure was recorded and controlled throughout each experiment. The amount of Berlin blue injected into each animal varied between 150 and 200 cc. The injection was started while the animal was still alive, but within five to ten seconds the animal was dead. Speed is an important factor because even a brief delay would allow asphyxia to dilate the vessels. After injection the brains were hardened, embedded and cut. Serial sections were made from a block cut to take in the whole surface of the brain at the level indicated in Fig. 1. In these sections, micrometer measurements were made of the injected capillaries in the *Area Occipitalis* (area 17 of Winkler and Potter)[10] in the *area postcentralis* (area 1 to 3) and in the *area insularis* (area 13 to 16). Knowing the area covered by the square micrometer scale, and the thickness of the section, the length of injected capillary per cubic volume of brain substance could be fairly accurately measured for each hemisphere. Technical errors such as those due to shrinkage

in fixation become insignificant when only comparative measurements of the right and left hemispheres are used. As the left cervical sympathetic nerve was cut in each case, the left hemisphere

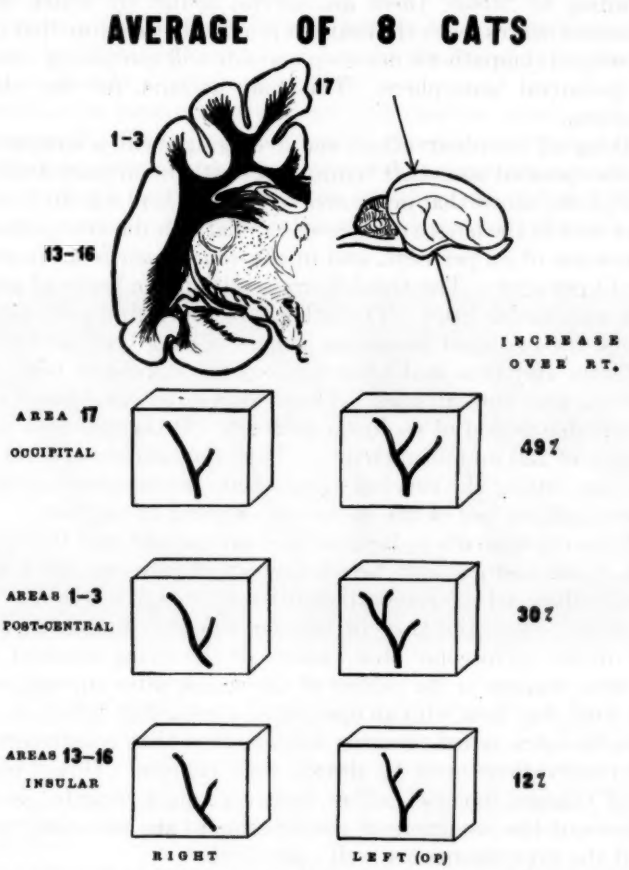


FIG. 1.—Diagram showing the increase in capillary bed in the left hemisphere after left cervical sympathectomy. Each block represents 100,000 cubic micra of cortical tissue, the bloodvessel drawn in represents the length of injected capillary measured in this block (about 62 micra in length, in the normal right hemisphere). After cutting the left cervical sympathetic nerve there is found by micrometry of the injected capillaries an increase of from 12 to 49 per cent in capillary bed in the left hemisphere. The arrows indicate the plane and level of section of the cat's brain. The sketch of the section at the left shows the location from which each of the three blocks of cortex were removed for microscopic examination.

is considered as the one experimented upon, and the right hemisphere is taken as the control.

Good preparations with even injections were obtained in 8 of the 10 animals. The capillary measurements showed that in every case more capillaries were open in the side operated upon (left hemi-

sphere) than in the normal right hemisphere. The greatest increase was in the *area occipitalis*, it was distinct but less marked in the *area postcentralis*, and very slight or negligible in the *area insularis*. According to Stöhr[11] there are several routes by which cerebral vasomotor nerves reach the brain; it is unlikely therefore that cutting the cervical sympathetic nerve on one side will completely denervate the ipsilateral hemisphere. This may account for the observed variations.

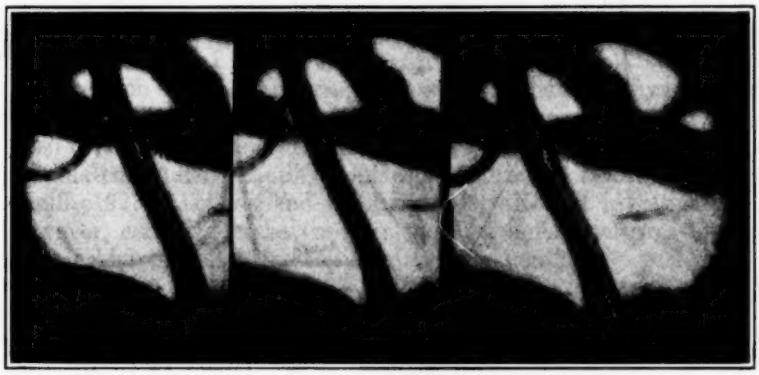
Taking all the observations and averaging them, a comparison of the side operated upon (left hemisphere) with the untreated side (right hemisphere) shows that in the *area occipitalis* there was an increase of 49 per cent in the length of injected capillary, in the *area postcentralis* an increase of 30 per cent, and in the *area insularis* an increase of only 12 per cent. The third figure is within the limits of probable error and means little. The other two are significant, especially because the two most important sources of error both tend to dilate capillaries and thus make less obvious the difference between the operated and normal sides. These sources of error are: (1) the unavoidable period of asphyxia at death; (2) the injection under a pressure of 220 mm. of mercury. Thus the conclusion seems justified that cutting the cervical sympathetic nerve causes an increase in the capillary bed of the ipsilateral cerebral hemisphere.

All the experiments so far described are indirect and therefore not entirely satisfactory, but there is a group of investigators who have directly observed the cerebral circulation through a trephine hole in the skull. Since the time of Brachet (1830)[12], numerous authors have made microscopic observations of the living cerebral vessels and seen changes in the caliber of the vessels after stimulation, but their work was done with an open skull, a procedure which so greatly alters the intracranial pressure relationships that conclusions from their observations must be drawn with caution. Direct observation of changes in vessel caliber, however, can be regarded as crucial evidence, if the conditions of the experiment are essentially normal, and if the experiments are well controlled.

A window in the skull was first introduced by Ravina (1811).[13] Cushing (1901)[14] employed it to watch the effects of increased intracranial pressure. More recently Forbes (1928)[15] has greatly improved the technique by adding a washout system beneath the window, by applying micrometry and microphotography to the vessels observed, and by concomitantly recording arterial and cerebrospinal-fluid pressures. The observations made by Forbes and Wolff (1928)[8,16] bring strong evidence to support the theory of vasomotor control. The pial vessels are seen to contract immediately after stimulation of the cervical sympathetic nerve and to dilate after stimulation of the central end of the cut vagus (see Fig. 2). During these reactions the systemic arterial pressure either remains constant, or rises during cerebral vasoconstriction and falls during cerebral vasodilatation.

Changes in the pressure of the cerebrospinal fluid in general parallel sudden changes in the diameter of the arteries, the pressure rising with dilatation and falling with constriction (see Fig. 3). These observations definitely controvert L. Hill's statement that the cerebral circulation passively follows changes in the systemic arterial pressure; they also add convincing data to the already considerable evidence of Weber, Hürthle and others.

In addition to experiments on nerve stimulation, much work has been done on the effect of adrenalin on the vessels of the brain. This, as a method for determining the presence of vasomotor nerves, is not entirely satisfactory, although such an authority as Gaskell (1916)[17] says that the action of adrenalin has proved the existence of vaso-



A *B* *C*

FIG. 2.—Photomicrographs of a pial artery taken through a window in the skull of a cat. *A*, two minutes before sympathetic stimulation. The artery is 58 microns in diameter. *B*, 40 seconds after a 60-second faradic stimulation of the left cervical sympathetic nerve (coil distance, 9 cm.). The artery shows a constriction amounting to 15 per cent of its initial diameter. *C*, at the end of a 60-second faradic stimulation of the left vagus nerve (coil distance, 9 cm.). The artery has dilated to 63 microns in diameter, which is 7 per cent larger than before the sympathetic stimulation. (See Forbes and Wolff.[8])

constrictor nerves in the brain. Schilf (1926)[18] is of the opinion that the action of adrenalin in itself cannot be used as a proof of the presence of vasoconstrictor nerves. Such interesting work as that of Wiggers (1905),[19] who showed by perfusion of an excised brain that adrenalin decreased the outflow, should only be used as corroborative evidence of the existence of vasomotor nerves. The recent experiments of Gruber and Roberts (1926)[20] explain the former conflicting evidence in this field; apparently the dilatation of cerebral vessels following application of "adrenalin" recorded by several observers was due to the use of acid solutions, or to chloretone. Pure adrenalin alkaloid causes vasoconstriction if the solution is not acid.

Thus there is good evidence that the cerebral vessels contract on stimulation of the cervical sympathetic nerve, that they lose their tone and dilate when that nerve is cut, and that they dilate when the central end of the vagus nerve is stimulated. In other words, the

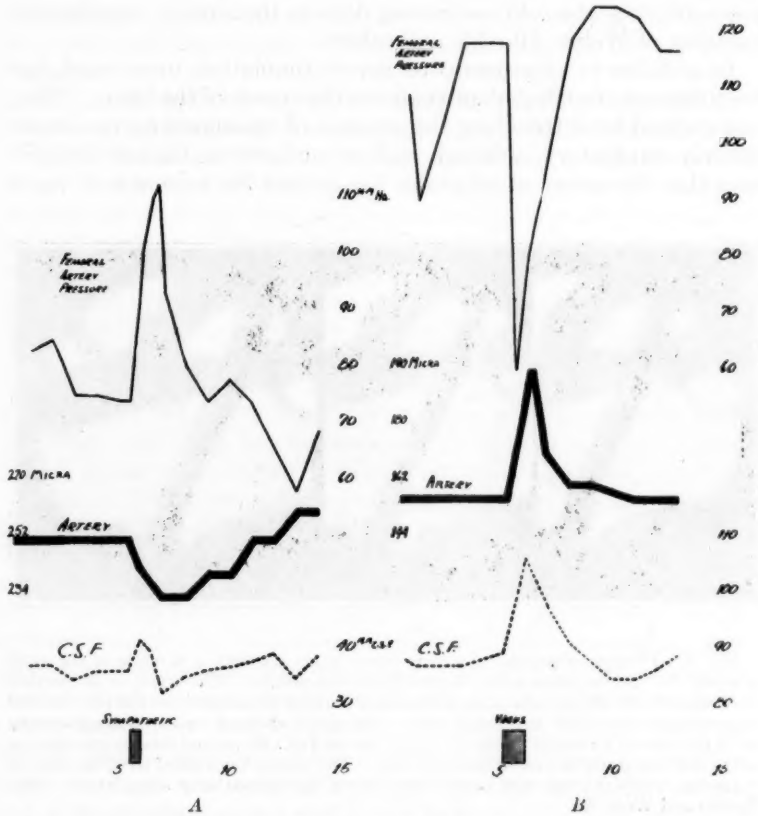


FIG. 3.—Two experiments by Forbes and Wolff showing the effects of (*A*) sympathetic and (*B*) vagal stimulation. Time is given on the abscissa in minutes. Faradic stimulation was applied to the nerves in the neck during the time covered by the shaded quadrangles. The lower dotted line gives the intracranial pressure measured in millimeters of cerebrospinal fluid registering in a manometer attached to a needle in the cisterna magna. The heavy middle line shows the changes in the diameter of the pial artery as measured under the microscope in micra. The upper line shows the variations in femoral artery pressure measured in millimeters of mercury. It is obvious that the changes in caliber of the pial artery are not only independent of, but in spite of, the changes in the systemic arterial pressure. (For other experiments and details see Forbes and Wolff, Arch. Neurol. and Psychiat., 1928, **19**, 1057–1086.)

bloodvessels of the brain react in the same way as vessels in other organs. It may well be that they react less strongly. Forbes and Wolff observed in the small pial arterioles an average reduction of diameter of only 8.5 per cent on sympathetic stimulation, and a

dilatation on vagal stimulation averaging 22 per cent of the diameter. From the functional standpoint, however, this is far from an insignificant change, for according to Poiseuille's Law (1842)[24] the minute-volume flow through a capillary tube of given length varies directly with the fourth power of the diameter of the tube. With a 22 per cent increase in diameter, therefore, there would be an almost 150 per cent increase in blood flow, that is the minute-volume would become two and a half times as great.

Summary. Taking all this evidence into consideration, it would seem that vasomotor control of at least the superficial cerebral vessels is now established. One must be guarded, however, in drawing clinical conclusions. Physiologically, it has been shown that pial vessels may constrict or dilate in response to appropriate stimulation, but in anesthetized animals the changes are not of great magnitude, and may be overcome by large variations in systemic pressures. L. Hill's statement, strictly speaking, still holds: "There is no evidence of a causation of cerebral anemia by spasm of the cerebral arteries." Real, obliterating angiospasm has only been experimentally observed when vessels are strongly and locally stimulated under nonphysiological conditions (Florey, 1925;[21] Wolff, 1927;[22] Lennox and Cobb, 1928.[23]) Recent investigations, however, certainly make vascular spasm a much more reasonable working hypothesis than it was thirty years ago.

REFERENCES.

1. Bayliss, W. M.: Principles of General Physiology, London, Longmans, Green & Co., 1924, p. 484.
2. Cecil, R. L.: A Text-book of Medicine, London, W. B. Saunders Company, 1927, p. 1304.
3. Hill, L.: The Physiology and Pathology of Cerebral Circulation, London, J. and A. Churchill Company, 1896.
4. Weber, E.: Ueber die Selbständigkeit des Gehirns in der Regulierung seiner Blutversorgung, Arch. f. Physiol., 1908, pp. 457–536.
5. Müller, W., and Siebeck, R.: Ueber die Vasomotoren des Gehirns, Ztschr. f. exper. Pathol. u. Therap., 1907, **4**, 57.
6. Hürthle, K.: Untersuchungen über die Innervation der Hirngefässe, Arch. f. d. ges. Physiol., 1889, **44**, 561–618.
7. Tigerstedt: Physiologie des Kreislaufes (2d edition), Berlin und Leipzig, Walter de Gruyter & Co., 1923, vol. **4**.
8. Forbes, H. S., and Wolff, H. G.: Vasomotor Control of Cerebral Vessels, Arch. Neurol. and Psychiat., 1928, **19**, 1057–1086.
9. Talbott, J. H., Wolff, H. G., and Cobb, Stanley: The Cerebral Circulation: VII. Changes in Cerebral Capillary-bed following Cervical Sympathectomy, Arch. Neurol. and Psychiat. (In press.)
10. Winkler, C., and Potter, A.: An Anatomical Guide to Experimental Research on the Cat's Brain, Amsterdam, W. Versluys, 1914.
11. Stöhr, P.: Zeitschr. f. Anat. u. entwicklungs Gesch., 1922, **63**, 562.
12. Brachet, C.: Recherches experimentales sur les fonctions de système nerveux ganglionaire et son application à la pathologie, 1830.
13. Ravina, A. F.: Specimen de motu cerebri, Mém. de l'Acad. des sci. Turin, 1811–1812, p. 61.
14. Cushing, H.: Concerning a Definite Regulatory Mechanism of the Vasomotor Center which Controls Blood-pressure during Cerebral Compression, Bull. Johns Hopkins Hosp., 1901, **12**, 290.

15. Forbes, H. S.: The Cerebral Circulation: II. Observation and Measurement of Pial Vessels, Arch. Neurol. and Psychiat., 1928, **19**, 751–761.
16. Forbes, H. S., and Wolff, H. G.: Cerebral Circulatory Mechanisms: Effect of Hypertonic Solutions, Arch. Neurol. and Psychiat., 1928, **20**, 73–82.
17. Gaskell, W. H.: The Involuntary Nervous System, London, Longmans, Green & Co., 1916, p. 48.
18. Schilf, E.: Das Autonome Nervensystem, Leipzig, George Thieme (Pub.), 1926, pp. 104–105.
19. Wiggers, C. J.: On the Action of Adrenalin on the Cerebral Vessels, Am. J. Physiol., 1905, **14**, 452–465.
20. Gruber, C. M., and Roberts, S. J.: Effect of Phenobarbital and Some Other Barbituric Acid Derivatives on Cerebral Circulation, J. Pharmacol. and Exper. Therap., 1926, **27**, 327–334.
21. Florey, H.: The Circulation of the Blood in the Cerebral Cortex, Brain, 1925, **48**, 43–64.
22. Wolff, H. G.: Personal communication, 1927.
23. Lennox, W. G., and Cobb, Stanley: "Epilepsy," Medicine Monograph, vol. **14**, Baltimore, Williams & Wilkins Company, 1928.
24. Poiseuille: Compt. rend., 1842, **15**, 1167 (see Bingham, Eugene C.: Fluidity and Plasticity, New York, McGraw-Hill, 1922, p. 406).

LYMPHATIC ABSORPTION OF PARTICULATE MATTER THROUGH THE NORMAL AND THE PARALYZED DIAPHRAGM: AN EXPERIMENTAL STUDY.*

By Willis S. Lemon, M.D.,
DIVISION OF MEDICINE, THE MAYO CLINIC,
AND
George M. Higgins, Ph.D.,
DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY, THE MAYO FOUNDATION, ROCHESTER, MINN.

In mammals, the diaphragm reaches its highest state of development and its functions are well defined and important. It contracts rhythmically and automatically with inspiration, increases the long diameter of the thorax, produces an increased intrapleural negative pressure and at the same time raises the intraäbdominal positive pressure. It relaxes and the results are reversed. By this muscular action it has affected both the function of respiration and of circulation. Increase in negativity of pressure in the thorax brings air into the lungs and blood from the periphery through veins into the heart. Its voluntary contraction provides for an increase in intraäbdominal pressure many times greater than that produced by its rhythmic action. This function not only permits extrusion of matter from the abdominal viscera, but at the same time prevents the increased pressure from embarrassing the action of the heart and lungs. It is a partition dividing the celom into two compartments, and as such it is a distinguishing characteristic of mammals. The partition, is

* Read before the Association of American Physicians, Atlantic City, New Jersey, May 7 to 8, 1929.

pierced to permit continuity of vascular, alimentary and nervous structures. It is also permeable to permit the flow of fluids through channels, some of which normally are visible and others invisible: the lymph ducts and the lymph capillaries. To determine the nature of this flow from its source to its ultimate connection with the blood-circulatory system has been the purpose of this experimental study.

There was occasion for investigation because of clinical problems that long have remained unsolved. We wished to know: (1) why the base of the right lung suffers disease following abdominal operations, especially when the organs in the upper part of the abdomen are disturbed; (2) why infections of the peritoneum almost invariably cause an inflammatory response in the pleura, and (3) why pleural infection rarely involves the peritoneum. The solution, in whole or in part, of these problems depends on an investigation of lymphatic absorption. Fortunately, the diaphragm is an ideal structure on which to pursue such an investigtion. It is a bilateral structure, each leaf of which is supplied by a single motor nerve. The factors of pressure and of muscular contractile movements, thought to be of significance in influencing the onset of postoperative phenomena, can be controlled at will by evulsion of one or of both phrenic nerves. The lymphatic drainage through a normal muscle may then be contrasted with that of a totally paralyzed one, and the relative speed of absorption and the quantity of absorbed material may be observed, as well as the vessels through which particulate matter flows. Only a proper medium is necessary. The medium must act as an indicator, and it must be particulate in character so that its absorption will simulate that of bacteria.

In the year previous to the start of this investigation, one of us (Higgins) with Graham[1] established five chief routes by which such particulate matter as we wished to employ might pass through the diaphragm. They found that "hydrokollag 300," a suspension of finely particulate graphite, was the most suitable medium, not only because it is black but also because it is a homogeneous mass of particles many times smaller than erythrocytes. By introducing this substance into the peritoneal cavity, they were able to allow the normal absorptive processes to fill the lymphatic vessels on the pleural surface of the diaphragm and the associated channels. This made visible the channels and made the direction of flow apparent. They believed that about 80 per cent of the material which passed through the diaphragm was carried by the lymphatic plexus of vessels which lies beneath the pleural surface of the diaphragm to the ventral surface of the sternum. From there it was transported to the large substernal lymph nodes which lie beneath the manubrium. The efferent vessels of these substernal nodes drain into the thoracic duct near its venous confluence, into the right lymphatic duct at the jugulo-

subclavian confluence, or indirectly through paratracheal mediastinal lymph nodes and thence to the thoracic duct. The system from the diaphragm to the substernal nodes was described as being plexiform, with loops of vessels passing from one side to the other. The plexiform nature of the vessels was especially noticeable after the vessels had passed the lymph nodes that lie in the spaces between the attachment of the first to the third ribs.

A second, or pulmonary, route that the material might take was found to be by way of a lymphatic vessel that passed backward over the vault of the diaphragm, thence upward parallel to the vagus to the nodes at the hilum of the lung. These in turn were connected by a plexus of vessels with the nodes in the arch of the aorta. Thence the course was to the paratracheal nodes which ultimately are joined, by small vessels, with the thoracic duct. In this course, there were tributaries that bridged across from side to side, making possible a final entry of the lymph either into both the right cervical or into the thoracic duct. They also described a small vessel passing upward, parallel to the phrenic nerve and vessels, into a paratracheal mediastinal lymph node on the ventral surface of the trachea, anterior to the arch of the aorta.

The third route described was by way of tributaries that passed over the vault of the diaphragm and thence cephalad on the posterior wall of the thorax to unite with the thoracic duct.

Finally, they described two groups of vessels that passed backward over the vault of the diaphragm and pierced it. One of these groups of vessels led to retroperitoneal lymph nodes in the neighborhood of the kidneys and the other to the large nodes in the splenic mesentery. All of these nodes were found to be directly connected, by lymphatic vessels, with the receptaculum chyli.

Material and Methods. In our study, we were desirous not only of repeating this work, but also of carrying the investigation further. We wished to determine the route and volume of drainage through paralyzed muscle and if possible to discover the mechanism that permitted particulate matter to pass through the muscular partition and into definite channels. The experiments were divided into 8 groups; dogs only were studied, and hydrokollag was the material injected in all but 2 cases. In these 2 cases, carmin and trypan blue were used.

Three dogs of the first group were anesthetized with ether and were operated on with the observance of careful surgical technique. The thorax was opened so that the movements of the diaphragm were visible. Then hydrokollag was injected into the peritoneal cavity and absorption into the subpleural lymphatics was observed. In other dogs of this group, a similar operation was performed; but previous to injecting the particulate matter, evulsion of the phrenic nerve was carried out, and the effect scrutinized. Later, hydrokollag was injected into the peritoneal cavity and its absorption into the

subpleural lymphatic vessels was observed both as to the time and degree of their filling.

The ten dogs of the second group underwent right phrenic neurectomy, at variable periods of time, from one day to eight months previous to the injection. All dogs were examined by fluoroscopic inspection before injection to be certain that the resulting paralysis was satisfactory and complete.

The three dogs of the third group were similarly operated on except that the phrenic neurectomy was done on the left side. The time previous to injection of hydrokollag into the peritoneal cavity varied in this group from one to three months.

The seven dogs in the fourth group underwent bilateral phrenic neurectomy from two to seven months before the absorption experiments were started. Otherwise, the technique was the same as in the other groups.

In the fifth group of six dogs, injection was made in the pleural cavity rather than in the peritoneal cavity.

In the sixth group, the pericardial space was injected.

In the seventh group of three dogs, operative work was not done, but the animals were fed melted butter in which hydrokollag, sudan III or trypan blue was intimately mixed.

In the eighth group of seven dogs, the injections were made directly into the cisterna chyli, into the descending lymphatic vessels lying on the posterior thoracic wall, or into the lymph vessels on the pleural surface of the diaphragm.

Results of Injection into the Peritoneal Cavity. The dogs were anesthetized and the ribs separated so that a view could be had of the movement of the diaphragm.

Nerve Supply to Diaphragm Intact.—In this group neither phrenic nerve was disturbed. It could be seen that the hemidiaphragm, under observation, moved normally with each inspiration. Hydrokollag was injected into the peritoneal space in amounts of from 30 to 40 cc., depending on the size of the dog. Within a period of three to four minutes, the lymphatic plexus on the dorsal surface of the diaphragm began to fill with the blackened material and the flow over the vault of the diaphragm was rapid and in the direction of the sternum. Most of the graphite passed forward into the substernal space and was lost to view. The filling of the lymphatics in the posterior portion of the diaphragm was less easily visualized and the direction of flow could not be easily determined. In other animals of this group, one phrenic nerve was severed before the material was injected into the peritoneal cavity. The immediate effect of division of either phrenic nerve was sudden paralysis and absence of movement of the leaf of the diaphragm on the side on which the nerve was severed. The muscle and the nerve were irritable and could be stimulated by mechanical measures. A marked contraction appeared on stimulation of the distal, cut end of

the nerve or when the muscle was directly irritated. However, when stimulation was not applied, the muscle was in a relaxed condition. When hydrokollag was introduced into the peritoneal cavity, it was seen that the period of time for filling the subpleural lymphatic plexus under observation was delayed. It usually could be seen filling the vessels ten to fifteen minutes after its introduction into the peritoneal cavity.

Right Hemidiaphragmatic Paralysis. In the second series of dogs, in which right phrenic neurectomy had been done at various periods preceding the neurectomy, examination with the fluoroscope was done as a routine to determine, before the intraperitoneal injection, whether or not perfect paralysis had occurred. In all instances, the right leaf of the diaphragm was high within the thorax and either had not shown evidence of movement with respiration or moved slightly in a paradoxic direction. The animals were injected forty minutes before they were killed by overetherization. At necropsy, the chest was opened by lateral incisions through the costosternal junctures, and the sternum itself was raised and carried downward, but it was not severed from the diaphragmatic attachments at the costal margins. Then both halves of the diaphragm could be seen. The appearance on the right side varied from normal to one of advanced atrophy, depending on the length of time that had elapsed between phrenic neurectomy and the intraperitoneal injection. Up to a period of approximately two weeks, there was no visible evidence, either in its thickness, color or opacity, that the muscle was paralyzed. However, it retained marked irritability, so that stimulation of the muscle itself, or of the distal end of the cut nerve, caused more vigorous contraction than was found when the same interference was used on the normal side. The degree of irritability, however, decreased with the passage of each day until a period of two weeks had passed; then the irritability was markedly lessened or lost, and the muscle became more flaccid, attenuated and less opaque than normal. In the groups in which neurectomy had been done eight months previous to the injection, the muscular tissue was so atonic that it had become transparent and the muscular fibers had lost their color to such an extent that it was only with great difficulty that one could distinguish the division between the central tendon and the muscular portion. The atrophy in every instance was limited to exactly one leaf of the diaphragm; the whole hemidiaphragm, from center to periphery, was paralyzed and there was neither evidence of nerves crossing from the uninjured to the paralyzed side nor of regeneration of nerves on the paralyzed side.

In normal animals, the lymphatic plexus on the right side is much more pronounced than it is on the left. This likewise is true, even though the muscle on the right is paralyzed and that on the left normal, and the direction of the lymphatic current in these animals is the same as that in normal dogs. All the five principal paths

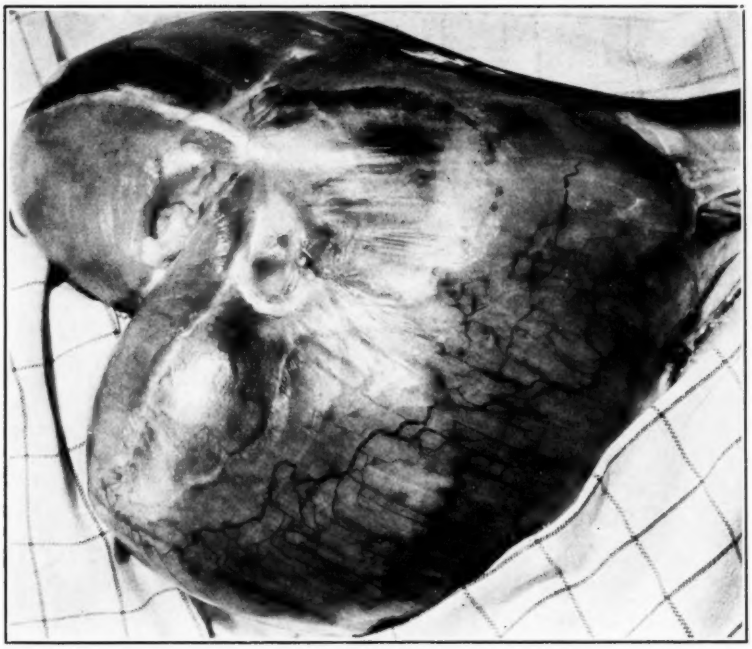


FIG. 1.—Lymphatic drainage on the pleural surface of the right hemidiaphragm, forty-five minutes after peritoneal injection in a dog on which right phrenicotomy had been performed four days before.

FIG. 2.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite may be noted in subserous lymph vessels (corrosive acetic fixation, ×100).

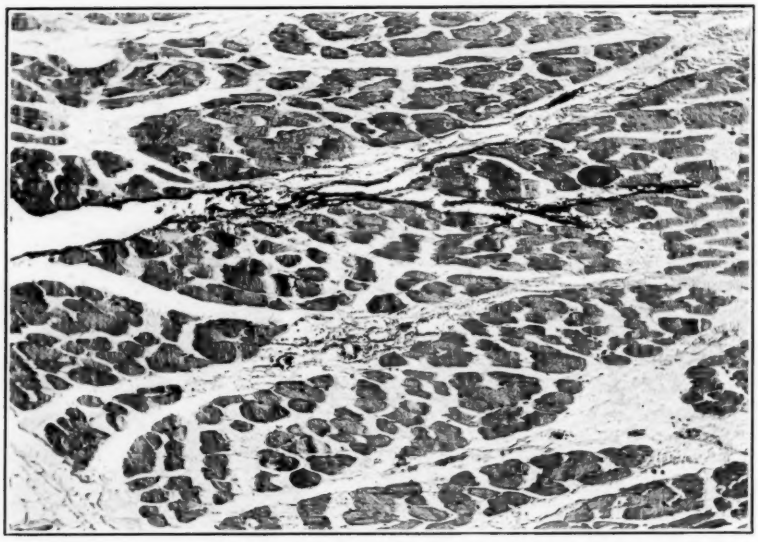


FIG. 3.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite may be noted in channels coursing through the diaphragm (corrosive acetic fixation, ×100).

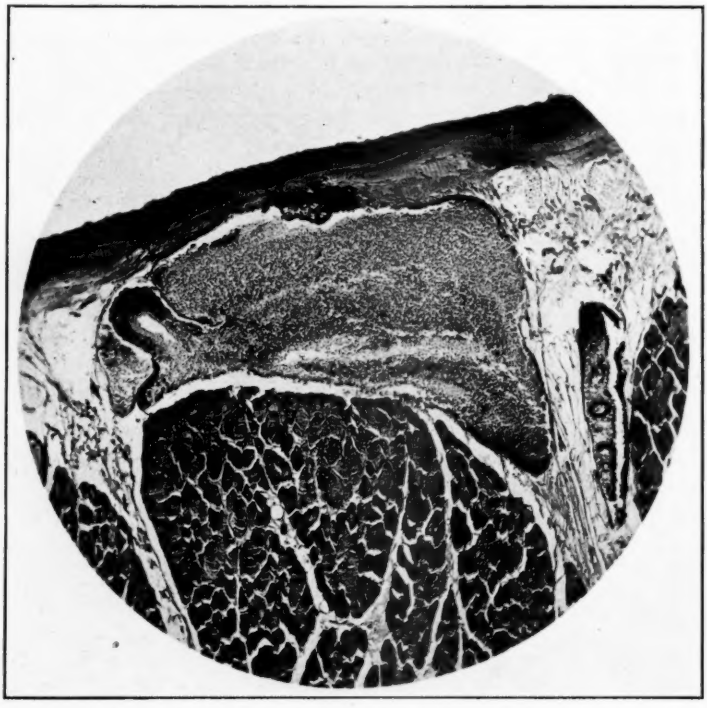


FIG. 4.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Large subpleural collecting lymph channel is filled with graphite (corrosive acetic fixation, ×100).

FIG. 5.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite granules may be seen passing through serosal surface to enter subserous channels (corrosive acetic fixation, ×100).

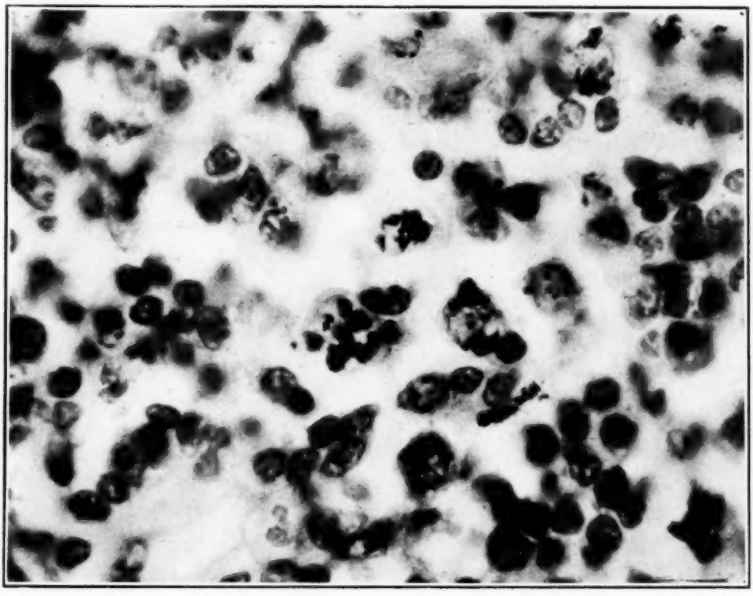


FIG. 6.—Section of large lymph node, adjacent to spleen in a dog forty-five minutes after the peritoneal injection of graphite. Large macrophages in gland containing graphite from lymph channels draining diaphragm may be noted (×1000).

can be demonstrated. Much the larger portion of the graphite passed forward over the vault of the diaphragm, upward through the plexus of lymphatics in the neighborhood of the internal mammary vessels and passed thence to the group of substernal lymph nodes from which small channels provided drainage into the thoracic duct. In the neighborhood of the substernal lymph nodes, the anastomosing vessels passed from one side to the other so that the lymph and particulate matter poured not only into the thoracic duct but a portion of it went also to the right cervical duct. In some cases, a descending lymphatic vessel could be found lying on the posterior wall of the thorax, and passing downward it penetrated the diaphragm and led into the lymph nodes that lie in the region of the kidney. This direct retroperitoneal drainage, however, occurred not only by this single vessel, but also by vessels passing over and downward across the vault of the diaphragm posteriorly. Either independently or after confluence with the descending vessel, these channels entered the same nodes in the region of the kidneys. The nodes themselves in turn were connected with the cisterna chyli by a variable number of small vessels. Also, there were instances in which small channels on the posterior surface of the diaphragm could be traced directly into the thoracic duct. They passed downward and entered the duct as it presented itself through the dorsal surface of the diaphragm. In other instances, the vessels after leaving the vault of the diaphragm passed upward on the posterior wall of the thorax before they entered the thoracic duct. Similarly, particularly on the left side, lymphatic vessels could be found which passed backward to a point anterior to the aortic opening in the diaphragm, and there, piercing the diaphragm, they entered the abdominal cavity and drained into a large lymph node or group of nodes lying in the splenic mesentery in the neighborhood of the pancreas. These nodes were directly connected, by a group of small vessels, with the cisterna chyli.

Left Hemidiaphragmatic Paralysis. When the left hemidiaphragm had been paralyzed for various periods of time preceding the intraperitoneal injection of hydrokollag, similar observations could be made, excepting that in no case was the drainage through the left side equal to that through the right side. The vessels themselves were smaller in size and fewer in number and apparently carried much smaller streams of particulate matter through them. In some instances, the amount was so small that the subpleural lymphatics were but faintly outlined. In others, the pattern could be very definitely made out, and all the main tracts that have been described could be readily shown.

Other channels were sometimes observed, although they were not always seen. The chief one of these subordinate channels was small and carried the particulate matter over the surface of the esophagus, parallel to the vagus, and upward to the lymph nodes

at the hilum of the lung. These were densely blackened and communicated by irregular channels with the lymph nodes at the arch of the aorta and the peritracheal nodes. From these nodes vessels deposited the hydrokollag in the lymphatic and thoracic ducts at their jugular confluences. On the left side, in one or two instances, very small vessels could be seen coursing over the diaphragm, passing upward along the phrenic nerve and vessels, and carrying its stream of particulate matter to a paratracheal lymph node. This vessel was never seen on the paralyzed side, probably because during evulsion of the phrenic nerve it had become obstructed.

Bilateral Diaphragmatic Paralysis. In the series of seven dogs on which bilateral phrenic neurectomy was done, the absorption through the diaphragm was delayed and the amount of material passing through the vessels seemed to be much less than in normal animals or in those with hemidiaphragmatic paralysis. There seemed to be no doubt that the contraction of the diaphragm itself had an influence in increasing the flow of lymph. Massage of the abdomen, pressure exerted on the abdomen, or muscular activity in the period of time elapsing between the injection of the particulate matter and necropsy did much to increase the drainage and to fill the plexus of subpleural lymphatics. All of the lymphatic tracts, however, were exactly the same as those in normal animals. The only variability from normal was in the speed of flow and amount of material carried.

In three animals that had undergone bilateral phrenic neurectomy three weeks before injection, 40 cc. of hydrokollag was injected into the peritoneal space and allowed to remain there for variable periods of time. Observations at necropsy were made ten, sixteen and twenty-four days, respectively, after the injection. When the abdomen was opened, it was found that the peritoneum was dry, but that the omentum was deeply stained with graphite which seemed to be caught in its meshes and fixed there. When the neck was opened, the thoracic duct was shown to contain only clear lymph, and its juncture with the vein could readily be demonstrated. Material taken from the thoracic duct failed to show any evidence of graphite. After the chest was opened, along the two sides of the sternum, the anterior mediastinum was seen to contain some blackened areas which indicated that hydrokollag had found its way into the lymphatics. The lymph vessels on the dorsal surface of the diaphragm, however, could be but indistinctly seen and did not contain graphite. The diaphragm itself had the same appearance, both on the ventral and on the dorsal surface, and it was blackened in patches which represented an accumulation of the pigment between the muscle bundles. The muscle in all three of these cases was thoroughly paralyzed and translucent. The substernal muscles were deeply and diffusely injected with the graphite, but showed an accumulation of material running in indistinct lines toward

the lymphatic vessels that lay beneath them and passed upward into the group of substernal lymph nodes. These were markedly enlarged and densely blackened. All the lymph nodes in the neighborhood of the trachea, in the region of the aortic arch and about the hilum of the lung were heavily infiltrated with graphite. The two lymph nodes in the region of the kidney and the one in the region of the spleen were also densely infiltrated and markedly enlarged; some of them measured 3.75 by 0.5 cm. These observations suggested that the lymphatics had drained all of the particulate matter possible into the lymph nodes and thence to the venous confluences of the lymphatic ducts. However, when these were overfilled further absorption failed to take place and the intervening lymphatic chains were emptied and could not be traced at necropsy. In the dog that had been injected sixteen days previous to necropsy, the diaphragm was more densely filled with hydrokollag than in the earlier experiment and the intercostal muscles lying between the seventh and eighth costal margins were deeply infiltrated. The infiltration pointed upward toward the median line and seemed to show a connection between the intercostal muscles themselves and the substernal muscles. There also was slight infiltration with hydrokollag in the anterior mediastinum in this animal. Infiltration could be made out in the pericardial attachment to the diaphragm and in the ligament of the left lung. The lung and visceral pleura were free from infiltration of any kind and the pericardium did not give evidence that it had absorbed particulate material. After removal of the diaphragm, it was seen that there were blackened areas throughout its fibrous portion and very fine vessels at the juncture of the fibrous with the muscular portion joined with the lymphatics in that region. In the early experiments, we were unable to find any similar evidence of absorption through the fibrous areas of the diaphragm.

Systemic Fate of the Particulate Matter in all Experiments with Intraperitoneal Injection. In all instances of peritoneal injection, regardless of the operation done on the phrenic nerve, the peritoneal surface of the diaphragm bore a smoky appearance. The graphite was distributed uniformly over the surface and attached to it. The fluid removed from the abdominal cavity proved that some of the graphite was free and that some was included within phagocytic cells. Some particles of graphite from the lymphatic plexus on the pleural surface of the diaphragm were found to be floating freely in lymph and some were included in phagocytic cells. The phagocytic cells were few in number. When the thoracic duct was blackened and was pouring its contents into the venous stream, it contained both free particles of graphite and particles enclosed in phagocytic cells, but the proportion enclosed in cells was much larger than that in the lymphatic vessels of the diaphragm. The blood stream itself contained free graphite but it also contained cells packed with

particles which showed that phagocytosis had occurred. In some instances, the blackened lymph stream in the thoracic duct could be observed as it flowed into the veins within thirty to ninety minutes after the peritoneal injection. The tissue juice pressed from a cut surface of any of the lymph nodes contained graphite both in the free state and also enclosed in phagocytic cells. The greater amount was intracellular.

Results of Injection into the Pleural Space and the Pericardium. Injections that were made into the pleural cavity were done to determine whether or not absorption would take place through the pleural surface of the diaphragm. There was not an instance in which the visceral pleura of the lungs or the pleural surface of the diaphragm showed any evidence whatever of absorption. The lymph nodes in the region of the kidneys, however, were blackened, probably because of the presence of the descending vessel that lies on the dorsal aspect of the thorax. The absorption was not through the diaphragm itself. The subpleural lymphatic plexuses were always free of the medium and hydrokollag was not present between the muscle bundles or on the peritoneal surface of the diaphragm. This particular type of experiment, in which the pleural cavity was injected, is incomplete and will be the subject of further investigation. It was done at this time simply to determine whether or not absorption occurred through the pleural as well as though the peritoneal surface of the diaphragm. The same is true of experiments in which injections were made into the pericardium.

Results of Feeding Dyed Food. In the feeding experiments, the only significant observation that could be made was that absorption did not occur through the diaphragm itself. All of the absorption appeared within the thoracic duct. When the food was stained with sudan III, all of the lymphatics of the abdomen were stained pink, the cisterna chyli itself was filled with pink lymph, and the thoracic duct poured its colored lymph into the blood stream

Results with Injection into the Lymphatic Apparatus. In all of the experiments that have been described previously, the course of the lymphatic stream was determined by the natural absorption mechanism of the body. In the final group of experiments, the normal courses that had been observed were made more clear by injection into the lymphatic channels. These were of two types: injections into the cisterna chyli and injections into descending lymphatic vessels of the thorax.

Injections of the particulate matter directly into the cisterna chyli outlined the passage of the lymph through the thoracic duct and thence into the blood stream. In some instances, the tributaries were filled and the connection between the thoracic duct and the posterior intercostal lymph nodes could be discovered. In other instances, vessels not commonly seen passed directly from the thoracic duct to the nodes at the hilum of the lung. The connecting

lymph channels between the hilar nodes and the chain of lymph nodes along the trachea could be filled, and the course could be followed to the juncture with the duct at its confluence with the veins. When the descending lymphatic vessels in the posterior wall of the thorax were injected, the lymphatic tract could be followed easily as it pierced the posterior attachment of the diaphragm and passed downward to the lymph nodes in the neighborhood of the kidneys.

The same result could be obtained if the appropriate trunks that passed downward over the vault of the diaphragm were injected. Their connection with the retroperitoneal lymph nodes could easily be demonstrated. Likewise the lymphatic vessels passing backward to the anterior surface of the aorta could be injected and followed directly to the lymph nodes lying in the splenic mesentery. When the several groups of lymph nodes were injected the tiny vessels connecting them with the cisterna chyli could be traced (Figs. 1 to 6).

Comment. We have found it difficult to correlate experimental data with clinical observations of disease in the lower lobe of the right lung on the basis of the lymphatic drainage. This is particularly true because we were unable to discover at any time lymphatic tracts within the lung through which the current coursed toward the periphery. There was no difficulty in discovering the course of lymph from the peritoneum to the hilar lymph nodes, but the course beyond, within the lung, was not evident. This is probably because the lymphatics within the lung flow toward the hilum. To ascribe infection to a lymphatic route would force one to admit that the infection spread into the lung against the normal current. Experimentally, we have been unable to force lymph through channels in the direction opposite to the normal flow. The lymphatic vessel itself ruptures before the valves give way. However, the problem of infection within the lung is more or less an academic one as far as the source of infection is concerned. We were able to discover that particulate matter passed through the diaphragm within a period of three to five minutes, but it also was found in the blood stream within thirty to ninety minutes. The period between the peritoneal injection and the finding of particulate material in the blood current is too short to permit one to distinguish, from a clinical standpoint, between lymphatic and blood-borne infections.

The circumstances regarding the inflammatory response in the pleura are somewhat more easily understood. The plexus of lymphatic vessels fills very rapidly, and the lymph, carrying particulate material, is separated from the pleura only by the pleural mesothelium. Therefore, by mere continuity of tissue, the infection might readily set up inflammatory reaction of the pleura, and cause an effusion to appear within the pleural cavity. This would be more likely to occur on the right side because of the much larger lymphatic

drainage—through the right portion of the diaphragm. It is significant that the lymphatics of the right leaf of the diaphragm carry a greater amount of material than those of the left, even when the muscle of the left side is normal and that of the right side is paralyzed. It is also significant, however, that the flow does not appear until a later period when the muscle of the diaphragm is functionless.

Another problem that seemed to us of significance before we started the work had to do with the rarity with which pleural infection involves the peritoneum. The solution is not at all evident from our experimental work. We are hoping that when the work on pleural injections is completed, something more may be said regarding the problem. The only facts we have at present are two: first, the pleural covering of the diaphragm does not absorb material injected into the pleural space; second, the descending lymphatic vessels carry particulate material from the thorax into the retroperitoneal space and the lymphatic vessels of the diaphragm carry it into the lymph nodes that lie in the splenic mesentery. It would seem possible that chronic infections, such as empyema, may obstruct the flow of lymph in which bacteria are being carried by sealing these tracts so that infection does not proceed into the peritoneum or the retroperitoneal region.

Summary and Conclusions. 1. These experiments on absorption through the normal and the paralyzed diaphragm confirm the observations made by Higgins and Graham that five main channels carry the particulate matter from the peritoneum upward through the thorax and into the blood stream.

2. These five routes and their functions are as follows: the first, the sternal route, which is much the most important, is that by which at least 80 per cent of the particulate material is carried. The second, the pulmonary route, is represented by a small vessel that empties its lymph into the nodes at the hilum of the lung and by a vessel that is parallel to the phrenic artery and nerve and carries its lymph to a node in the anterior mediastinum. The third route is through the thoracic duct which receives as tributaries small vessels that pass over the dorsal portion of the diaphragm and enter it in various positions along its course. The two remaining routes, the fourth and fifth, are represented first by vessels that pass over the dorsal surface of the diaphragm, pierce it, and empty their lymph into the lymph nodes in the region of the kidney, and second, by small vessels which also pass over the vault of the diaphragm to a point anterior to the aortic opening where they pierce the diaphragm and pass downward into the splenic mesentery and pour their contents into the lymphatic node in the region of the pancreas. All of the nodes which receive the tributaries are in turn connected by vessels with the receptaculum chyli.

3. The experiments also have demonstrated the presence of a descending thoracic vessel which passes downward over the posterior

wall of the thorax, sometimes receiving tributaries from the vessels of the posterior portion of the diaphragm and communicating with the lymph nodes in the region of the kidney.

4. The particulate matter seems to be taken up diffusely on the under surface of the diaphragm. It passes between the mesothelial cells of the peritoneum into tiny lymphatic vessels and thence is carried between the muscle bundles until it is deposited within the subpleural plexus of lymphatic vessels. This transfer from the peritoneal surface to the pleural surface is rapid; it requires only from three to five minutes in normal muscle and from ten to twelve minutes in paralyzed muscle.

5. The penetration of particulate matter into the blood stream is effected within a period of from thirty minutes to one and a half hours.

6. The lymph taken from the lymphatic vessels on the surface of the diaphragm is mainly found in a free state, although a few phagocytic cells also contain some of it. The material taken from lymph nodes is found mainly to be enclosed in phagocytic cells, although a slight amount is still free. That which comes later through the thoracic duct is mostly enclosed within the phagocytic cells, but some particles are still in a free state. When obtained from the blood, it is both in free state and enclosed in phagocytic cells. It is probable that the monocytes take up the free material very quickly after it has been passed into the blood stream.

7. There is no question but that normal muscular contraction of the diaphragm contributes much to the passage of the particulate matter through the diaphragm. Nevertheless, the difference in size of the lymphatics on the two leaves of the diaphragm also is important. The lymphatics on the right side are much larger and carry a much larger proportion of the lymphatic flow than those on the left. Even after paralysis of the right half of the diaphragm, the pattern discovered after the lapse of thirty minutes is more distinct on the paralyzed right side than on the normal left side. Absorption through the left half of the diaphragm, when that half is paralyzed, is insignificant. Often the vessels are but indistinctly outlined.

8. It is apparent from the evidence obtained in the prolonged absorption experiments that the primary flow of particulate matter stops as soon as the lymph nodes become choked with graphite.

9. It is our belief that the lymphatics of the diaphragm are concerned with absorption from the peritoneal space.

REFERENCE.

[1] Higgins, G. M. and Graham, A. S.: The Lymphatic Drainage from the Peritoneal Cavity in the Dog, Arch. Surg. (in press).

THYRONEURAL DYSTROPHY.

The Association of Congenital Myxedema with Mental and Neuromuscular Disorders.*

By Walter M. Kraus, A.M., M.D.,
ATTENDING NEUROLOGIST, MONTEFIORE HOSPITAL,

Samuel Brock, M.D.,
ASSOCIATE NEUROLOGIST, MONTEFIORE HOSPITAL,

AND

Paul Sloane, M.D.,
RESIDENT NEUROLOGIST, MONTEFIORE HOSPITAL,
NEW YORK.

(From the Neurologic Department of Montefiore Hospital, New York City.)

The well-known association of mental defect and thyroid insufficiency indicates the close interdependency during growth of the central nervous system and the thyroid gland. Cases of thyroid deficiency (cretinism, congenital myxedema) associated with neural defects other than mental have been rare. Well-known textbooks do not mention them. It will be shown in the following that thyroid deficiency may be associated with such brain defect as will lead to mental defect, and with disease of phylogenetically older neural structures. As a result, serious disorders of neuromuscular control, manifested in various grades of diplegia, ataxia, chorea, and so forth may coexist with thyroid insufficiency.

Historical Survey. The first note of the condition which we have found is in 1908, when McCarrison[1] first drew attention to "the frequent association of a definite train of nervous symptoms associated with cretinism. These symptoms were present in 71 cases among a total of 203 cretins, and appeared to me to constitute a definite type of disease to which I applied the term 'nervous cretinism.'" These cases were observed in British India, in the Chitral and Gilgit Valley. McCarrison pointed out that various degrees of cerebral diplegia were associated with the cretinism, and either the thyroid or cerebral manifestations might predominate almost to the exclusion of the other.

McCarrison further stated that "the signs of derangement of the central nervous system may vary from the slightest degrees of paraplegia to the most intense grades of spasticity, athetosis, fits and

* The diagnosis of these cases as belonging to the same group as those reported by McCarrison was made at Montefiore Hospital in 1922 by S. A. K. Wilson, M.D., of London, and some of the literature herein quoted was sent by him to one of us (W. M. K.) shortly thereafter. For this help we wish to express our thanks.

idiocy. Nystagmus, which is rare in the purely myxedematous forms, may be present in these cases, and squint is common."

In 1913, Crookshank,[2] in reporting a case of cretinism showing "ataxic paraplegia," observed that there are three varieties of nervous symptoms: (*a*) choreiform; (*b*) ataxic, (*c*) spastic. In the same year, Langmead[3] also reported a case.

In 1910, Manson[4] reported 2 cases of cretinism in twins, one of whom had epileptiform seizures and one cerebellar symptoms. Söderbergh's case,[5] published the same year, showed bilateral adiadochokinesis and cerebellar catalepsy of Babinski. These signs disappeared after thyroid medication. In 1914, Vetlesen[6] presented 3 cases in which myxedema and paralysis agitans were associated. In 1923, Barkman[7] published a case with symptoms of cerebellar and extrapyramidal disease. He believed that in myxedema there is a toxic effect upon the cerebellum and basal ganglions. The neural signs and symptoms disappeared under thyroid administration. In De Quervain's experience[8] the neural signs often ran parallel to the intensity of the symptoms of cretinism. Lundberg[9,10] described 7 cases with cerebellar signs. Eaves and Croll[11] reported a case of myxedema with convulsions. In most of these cases, beneficial results followed the administration of thyroid. On the other hand, after studying a series of 1700 feeble-minded children, Naville[12] believed that disturbances of the thyroid play no great part in the etiology of congenital diplegias. In 1922, Barlow[13] examined vestibular irritability in 15 cases of myxedema, and found that there was reduction of irritability of the eighth nerve. One large group of possibly related cases has been found, notably that reported by Chagas[14] in 1913. The majority of these cases, which Chagas attributed to the Trypanosoma cruzi, began in infancy ("premières années de leur existence").

Briefly, therefore, we are confronted with a disorder of the thyroid gland of congenital origin, associated not only with mental defect, but also with motility disorders of various kinds and severities. Before discussing the various aspects of this curious combination of endocrine and neural defect, we shall present 2 cases occurring in one family.

Two Case Histories. (R. and N.) *Family History.* The cases are a girl and a boy in a family of seven children, all the others of which are normal. The ages at present are twenty-nine, twenty-eight, twenty-six, twenty-four, twenty-one, nineteen and sixteen years. The oldest, R., a girl, is most severely affected; the next to youngest, N., a boy, but slightly. Indeed, if any comparison were made, it would be that R. shows less thyroid defect and more nervous defect, while N. shows the reverse. There is no thyroid or neural defect in the parents or in the history of the family. The mother and father are first cousins. The father is flat-footed, a fact which is of especial interest in connection with the foot deformities of R. and N.

CASE I.—*Development.* R., aged twenty-nine years. She has been ill since birth. Icterus neonatorum persisted for the first six months. She

walked for the first time at three years, talked at five years. The anterior fontanelle closed at seven years. Cretinism was diagnosed early, and R. has been given thyroid on and off for at least twenty years. She had scarlet fever, diphtheria, measles and frequent attacks of sore throat during childhood, but as far as can be discovered, these illnesses had no effect upon her condition. At the age of eight, R. went to school, but having remained in the same class for three years, she was put in ungraded classes, where she remained until the age of fifteen. She learned to read and write and do simple arithmetic. R. then went to work. She began to typewrite, became a typist, and continued at this occupation until the age of nineteen. She then worked in a factory, boxing neck-ties, until the age of twenty-one, when she stopped work. She has not done any since. At the age of twenty-four, she still showed unmistakable signs of mental defect. The menses began at seventeen years, but have been extremely irregular, often appearing only at two- and three-month intervals. Dyspnea on exertion and excessive perspiration at night have also been complained of for some time.

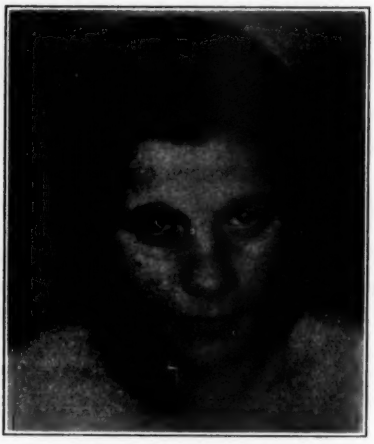


FIG. 1.—Facies in thyreoneural dystrophy (Case R). Note enlarged thyroid gland.

History of Neural Defects. At the age of eight, R. began to stutter. This remained about the same until 1920 (age twenty-one years) when it gradually became much worse. At that time there were also deformities of the feet and a peculiar unsteady gait. About 1922, spasmodic flexor movements of the right upper and later both lower extremities appeared.

R. states that at about the same time, she became subject to "fainting attacks" and that she would fall to the ground. There were no convulsions. She describes these attacks as first dizziness, then a feeling of twitching of the eyes, then a feeling of cold and then falling. "Afterward I do not know what happened to me." There is no tongue-biting, convulsion, incontinence or aura. She does get pale before fainting. While the patient was in Mount Sinai Hospital in 1921, these static seizures were observed by a nurse who found her lying in a heap on the floor. She was also found unconscious on the floor by her employers on several occasions. Frontal headaches and spells of dizziness are also complained of.

R. states that occasionally she has attacks of laughter without provocation. Cold hands and dry skin are stressed, together with frequent "choking" when eating solids or liquids.

R. has complained of very persistent constipation; this has been confirmed by observations made at Montefiore Hospital. All efforts to induce normal bowel movements have been unavailing. She states that she has attacks of vomiting, but these have never been observed in the hospital. Sharp epigastric pains occur, worse after meals and associated with some nausea. She has noted frequency of urination—eight to ten times a day, and twice at night.

Examination. 1. *General.* She is an overnourished, well-developed young woman, who looks her age, twenty-nine years. The skin is dry and of a yellowish hue; the lips exhibit good color at times, at others show definite pallor. The hair is dry. It is abundant upon the head. The axillary and pubic hair is normal. The throat and fauces are normal. Heart, lungs and abdomen are negative. The blood pressure is 100 systolic and 70 diastolic. There is no bony disorder and no spinal curvature. The thyroid is definitely enlarged and soft to the touch (Fig. 1).

The urine is normal, the blood Wassermann negative. The basal metabolism (1921) is −15. The hemoglobin is 95 per cent. Blood chemistry follows: Urea nitrogen, 18.2; incoagulable nitrogen, 42; uric acid, 3.9; creatinin, 2.2; cholesterin, 0.13; blood sugar, 0.090 per cent.

FIG. 2.—Dorsi-extension of the left big toe (Babinski sign) in Case R.

Roentgen ray report, December 17, 1920: "Stereoradiographic examination of the skull shows the sella turcica to be somewhat irregular, with atrophic posterior clinoid processes, apparently bridging over the entrance to the sella. The sphenoidal sinus appears very small. The bones of the skull are thick and do not show any signs of intracranial pressure, but there is a small area on the vertex of the skull which is rather suggestive of an atrophic process in the left parietal bone (fontanelle?)." "Examination of the hands shows a normal condition for her age."

2. *Neural. Cranial nerves:* Negative. *Sensation:* Normal for deep and cutaneous types. There is no Romberg or ataxia in the trunk or extremities. *Reflexes:* Normal except for the reaction of the great toe. It is almost constantly in extension on the left. When plantar stimulation is tried (Fig. 2) extension results on both right and left sides. *Motility:* There is no atrophy of muscles. Possibly R. is not as strong as her heavy build would lead one to expect. She stutters very markedly, and when speaking there are spasmodic, associated movements of the face and right upper extremity. The latter is involuntarily flexed. At times the same type of movement is noted in the left face and the left upper extremity in lesser degrees. Again, there are flexor movements of trunk and hips. While seated, the left leg is drawn up when speaking. In 1920, this was the only abnormality. In 1923 (age twenty-four years), she often had movements of the left extremities, and occasionally of the right lower when speaking.

This made her sway almost continually when she conversed. The movements also occur when she is not speaking. They recall athetosis on the one hand, chorea on the other. One is also reminded of certain cases of dystonia musculorum deformans.

FIG. 3.—Pes cavus in Case R (thyreoneural dystrophy).

The feet are both deformed and show the typical pes cavus seen in Friedreich's ataxia (Fig. 3). But there are no other signs of this condition, beyond the dorsiflexion of the great toes. The cavus is marked, the extension of the great toe at the proximal joint and flexion at the distal is well seen.

FIG. 4.—The broad feet in Case R (thyreoneural dystrophy).

The toes are clawlike, the fore part of the foot unusually wide (Fig. 4). Plantar stimulation elicits bilateral Babinski toe reflexes. The abdominal reflexes are diminished on the left. The gait is unsteady, and *the patient walks upon her toes* (Fig. 5). The foot posture recalls the "dromedary foot"

of dystonia musculorum deformans. There is perhaps some unsteadiness beyond this, but it is hard to determine. As has been noted, there is no Romberg. She can walk flat-footedly, but this is difficult, seems unnatural for her, and increases the unsteadiness of gait.

Such was the status of R. from 1921 to early 1923. Since that time she was observed over shorter or longer periods on five other occasions, namely, in July, 1923, December, 1924, March, 1925, August, 1927, and July, 1928. Brief reference will be made only to the *changes* occurring in her status.

In July, 1923, the following note was made: R. shows choreodystonic movements, affecting the shoulder and neck mainly, less evident in the lower extremities. There is marked up and down, and side-to-side movements of the head, and an almost constant rhythmical movement of pronation and supination while the hands are at rest. This recalls the tremor of

FIG. 5.—The tip-toe gait in Case R (thyreoneural dystrophy).

Parkinsonism. It is more marked on the right than on the left. There is a slight tendency toward flexion contracture in the fingers of the right hand. Hypotonia is present.

The left foot shows a typical equinovarus with extension of the first phalanges and flexion of the others; the right exhibits less marked extension of the first phalanges. There is a definite Babinski reflex on the left. The movements, especially the attitudinizing, are very reminiscent of Huntington's chorea.

Mentally, R. shows evidence of real intellectual defect. She answers all the questions in the ten-year-old scale, and almost all in the twelve. She has a mental age of eleven and a half years. She shows slight difficulty in retention. Her judgment is fairly good. Her associations are also fairly well executed. She shows no psychotic trends. Her emotional reaction is somewhat inadequate and excessive, but she shows no real evidence of conversion hysteria.

All other symptoms are the same but more marked. Diplopia is said to be associated with headaches. Occasional dysphagia is present with

regurgitation of food through nose and mouth. Recently dysuria has appeared. The spinal fluid is normal.

In December, 1924, generalized choreiform movements were noted, mainly on the right. Adiadochokinesis and rebound phenomena gave evidence of disorders of synergy in both upper extremities, more so on the right. The *R. Q.* was 0.78, 0.79. Basal metabolism was −18, −26.

By March, 1925, the continued thyroid therapy had caused some reduction in size of the thyroid. Its consistency was firmer. The movements, gait, feet, and so forth were the same. In addition, the muscles of the right corner of the mouth twitched slightly, and there were occasional movements of the lower jaw to the left. The entire head from time to time moved to one side, more to the right, with visible contractions of the sternocleidomastoid muscles. There were frequent arrhythmic-movements of the right shoulder and flexor movements of the hand. The entire body seemed to take part in these irregular movements.

In August, 1927, a depression of mood had set in, with much nausea and frequent vomiting. In addition to the above-mentioned movements, comment is made on a constant rhythmic movement of the right upper and lower extremities, of a Parkinsonian nature. Occasionally the amplitude increases markedly and the arm alternately flexes and extends at the elbow. The fingers are held flexed at the phalangeal joints. The thumb is adducted and flexed, and at times assumes the Parkinsonian attitude. The small finger is attitudinized in adduction and flexion. Occasionally, clonic movements of individual muscle groups are noted. Especially the toes of the right foot show rhythmic movements. There is alternate hypertonia and hypotonia, especially on the right side. The movements are very much exaggerated upon emotional disturbance.

In July, 1928, fits of crying and depression were noted. The choreiform movements were still more widespread. A bruised, torn condition of the external urinary meatus was the cause of the dysuria she complained of. The "fainting" attacks continued. *R. Q.* was 0.76, 0.75. Basal metabolic rate was −25 and −27.

Disturbing dreams (pursuit by strange men, daggers thrust into her, and so forth) indicated conflicts associated with high-grade emotional tensions. An attempt at psychoanalysis earlier in her illness (1921) had been of no avail.[1]

CASE II.—*Development.* N., aged fourteen years. Of this case, not so much can be said. Birth was normal. He did not sit up until the age of four years, could not stand until the age of five and a half years, and did not talk until the sixth year. The anterior fontanelle closed at the age of three. N. is extremely backward in school. He can read and write simple sentences and can add simple figures, but cannot multiply. He is very quiet at home, sits about, has no initiative, is dull and acts slowly.

History of Neural Defects. These are few. He laughs in rather silly fashion without provocation (mental defect). There is fecal and urinary incontinence.

Examination. 1. *General.* He is a cretin in appearance (Fig. 6*B*), much shorter than his brother, who is three years younger (Fig. 6*A*). There are no gross defects of development (hernias, etc.), but the hair on the back is abundant above the scapulæ. The hands are spadelike. The feet are deformed, namely, a moderate degree of pes cavus and slight extension of the proximal joints of the toes, with flexion at the distal (compare his foot, Fig. 7*B*, and that of his brother, aged eleven years, Fig. 7*A*. Also

[1] In May, 1929, the right lobe of the thyroid gland had enlarged to the size of a small orange. It interfered somewhat with breathing and surgical intervention was being considered.

A *B*

FIG. 6.—Case N (*B*) contrasted with his brother (*A*) three years younger.

A *B*

FIG. 7.—Contrast between the pes cavus of Case N (*B*) and his brother's normal foot (*A*).

compare with the foot of R., Figs. 3 and 4). There is the same abnormal width of the fore part of the foot as in R. Clawing of the toes is not noticeable. Tightness of the Achilles tendon limits dorsiflexion of the feet.

The teeth are abnormally spaced. The central incisors are very wide (½ cm.), while the space between them is about 4 mm. The teeth are poorly developed and much decayed. The tongue is not unusually large. The fauces and tonsils are normal. The heart, lungs and abdomen are negative. The form of the body shows an increased lumbar curvature with pot belly. The genitals are normal. The thyroid is slightly enlarged and soft. Both the isthmus and lateral lobes are easily palpated. The skin is dry. No pubic or axillary hair is seen. The hair of the head is dry and coarse. The eyebrows meet; over the temples a fine growth of hair almost reaches the lateral ends of the eyebrows.

2. *Neural. Cranial nerves:* Negative. *Sensation:* Normal. There is no ataxia or Romberg. *Reflexes:* Normal except in the toe reactions. On stimulation of the sole of the foot, there is either dorsiflexion of the great toe or no movement at all. The dorsiflexion is more often obtained on the left than on the right. The foot then recalls that of Friedreich's ataxia. It is interesting to note that the left side is more affected in R. When the patient is supine, both great toes are extended, the left more so than the right. One feels that the absence of erectness permits the reaction to appear more readily, indeed, spontaneously. When the left thigh is forcibly flexed, there occurs extension of the great toes on the left, but not on the right. When the test is tried on the right, extension occurs as before, on the left, and not on the right (crossed Babinski). Fanning of the toes is observed on the left, not on the right. Gordon and Oppenheim reflexes are not elicited; indeed it is interesting to note that extension of the great toe on the left first increased by flexion of the ipsilateral thigh and then by flexion of the contralateral thigh, is changed to flexion by both the Gordon and Oppenheim tests. The gait is waddling with small steps and a slightly broadened base. His speech is slow, pronunciation of words defective.

Discussion. *Family Occurrence.* Since congenital myxedema or cretinism is well known to occur in families, it is not surprising to find associated neural signs in 2 of a family of 7.

Etiology. 1. The relation of thyroid insufficiency in the mother probably bears a very definite relationship to the occurrence of the myxedema and cretinism in her children. Furthermore, it is probable that the time of incidence of the greatest thyroid deficiency in the mother during her pregnancy has a bearing upon the development of the brain of the fetus, and the adequate nutrition of its cells. If the greatest insufficiency occur at a time when the basal ganglions, for example, are undergoing their greatest development, it would be natural to expect a defect in their development, and thus in their function. Furthermore, various grades of glandular defect may condition quantitatively different neural changes The beneficial effect of thyroid therapy not only upon many cases of thyrogenic mental defect, but also upon many instances of the type here reported, indicates clearly the relationship of thyroid deficiency to cerebral development.

Another factor is insufficient maternal thyroid during the period of lactation. This is emphasized by McCarrison. He noted that his cases rarely showed signs until after lactation was, or should have been over, which he regards as evidence of deficient nutrition in general.

It would appear that the possibilities are these: (*a*) Insufficient maternal thyroid secretion during pregnancy with consequent neural defects in the offspring; (*b*) insufficient thyroid in the newborn uncompensated, due to insufficient thyroid in the maternal or other milk; (*c*) insufficient thyroid in the newborn, compensated for by the maternal milk. Such cases become hypothyroid after lactation is over.

In brief, therefore, deficient thyroid secretion during the critical periods of the development of the nervous system appears to be the cause of the disorders noted. Indeed, since Walter's experiments[15] show that the absence of the thyroid gland interferes with regeneration of peripheral nerves, it would seem that this gland influences the development of the peripheral, as well as the central nervous system.

2. The relation of the condition to infection has been discussed especially by Chagas,[14] who has maintained that his cases are dependent upon infection by the Trypanosoma cruzi. McCarrison believes it more likely that Chagas cases are primarily endemic cretinism or myxedema with secondary infection by trypanosomes. The cases here reported seem to bear out this contention. That intercurrent infections will aggravate congenital thyroid defect is well recognized, but it seems scarcely credible that a congenital thyroid defect in but 2 of 7 children could have been due to a chronic infection of the mother.

Age of Onset and Recognition. The age of recognition appears to be very early, as noted above, before the second year. The nervous symptoms may not be evident until late, as in the case of R. *The late onset of involuntary movements* in R. may be ascribed to one of two causes: First, a developmental abnormality of the basal ganglions due to a defective thyroid gland. The neural symptoms would be thus regarded as due to an abiotrophy comparable to that noted in Friedreich's ataxia. As a matter of fact, some of R.'s signs are reminiscent of that disease in which, also, the signs may not appear for a number of years after birth. Second, the work of Stern, Rapoport and Kremlew[16] shows that thyroid defect is associated with increased permeability of the blood—cerebrospinal fluid barrier for colloids. This would more readily permit the passage of toxic agents into the central nervous system of a hypothyroid individual. If this hypothesis be held, then an independent toxi-infectious agent may have been the causative factor for the neural phenomena in the case of R. This second theory would also explain the nonbeneficial effect of thyroid therapy in her case.

Sex. There is no sex limitation.

Relation of Neural Symptoms to the Thyroid Deficiency. The relation of the severity of the neural symptoms to the degree of glandular deficiency may vary greatly. As McCarrison has emphasized, in some cases, the myxedema is scarcely recognizable.

The effect of thyroid therapy upon the neural symptoms also may give evidence of this variability. In the two cases reported here, N. shows much more evidence of thyroid defect and much less evidence of neural disorder than R. Since N. has received relatively little thyroid therapy while R. has received a good deal over a long period, it is natural that she should show less endocrinic defect.

Mental State. The mental state requires little comment. It may vary from idiocy to almost no defect.

Paroxysmal States. These are extremely interesting and recall very closely those described by Ramsay Hunt[17] as static seizures. His description follows: "By static seizures I mean a form of epileptic seizure characterized by sudden loss of postural control." There is a brief loss of consciousness. Hunt states that he has only observed these fits in cases of idiopathic epilepsy. Here we have another disease in which static fits occur. They have also been seen in a case which, for want of a better name, may be designated as a striopyramidal syndrome. The partial loss of postural control in some cases of epidemic encephalitis of the Parkinsonian variety probably also belongs in the group of "static fits."

Diplegia, Chorea, Ataxia, Torticollis, Facial Spasm. Spastic diplegia has been the common finding in these cases—all grades from slight reflex changes to scissor-leg deformities. In neither R. nor N. was diplegia present; though in her gait R. now gives the impression of spasticity. The other choreiform and ataxic types seem less common. Though showing no evidence of being ataxic, R. gives that impression, due to her choreiform movements. Both cases show pathologic reflex changes (great toe), and foot deformities.

The choreic movements of R. are not unexpected in a group of cases some of which show typical diplegia, some chorea, and some ataxia. The association of stuttering with these movements has been noted. Her speech is like her movements, which are undoubtedly due to disease of the extrapyramidal systems. The unilateral onset followed later by bilateral involvement indicates progress of the condition in spite of fairly consistent thyroid therapy. In the cases of McCarrison, Langmead and Crookshank, improvement and even cure was noted under thyroid therapy. Obviously, the lack of thyroid plays a great part.

Stuttering. The stuttering brings up an intricate problem. This speech defect is so often attributed to functional disorders that the organic origin has been too little emphasized. It is probably true that a predisposing organic substrate, often familial, exists, even where the functional element predominates. We know now that careful search into the history of apparently exclusively hysterical conditions reveals a slight but definite history of organic disorder sufficient to cause the deviation of the functional disorder into a particular, definite groove. In R. it unquestionably was of organic origin. Its clear association with the spasmodic movements of the

face, trunk and extremities indicates a common basis. Such stuttering has been observed in other disorders clearly of organic nature, particularly in certain cases of epidemic encephalitis of the Parkinsonian variety.

Foot Deformities. The foot deformities have been of interest. What seems striking is the resemblance to the foot of Friedreich's ataxia. But even more striking is the fact that the deformities of the foot are due to overactivity of the intrinsic ventral muscles (pes cavus, and flexion of the toes at the proximal joints). The "ventral foot"[18] is common to many diseases, among which is diplegia. In a great number of diseases, one of which is here described, there is simply a release of a group of muscles having a definite common reaction. For a discussion of this matter *in extenso*, the reader is referred to other papers by Kraus.[19] What seems of greatest interest is that such deformities may occur as isolated, fragmentary manifestations of any of the forms of diplegia.

Babinski Sign. The occurrence of dorsiflexion of the great toes—a Babinski response in both cases, is striking, and recalls the findings of Chagas and McCarrison, who noted all degrees of involvement, from slight reflex changes to scissor-leg deformity. The dorsiflexion of the toes, like the foot deformities, represents a fragment of a more widespread condition.

Constipation and Enuresis. Constipation has been a conspicuous symptom throughout the observation of R. and has been very severe and resistant to treatment. It has been observed in these cases by McCarrison. Enuresis and frequency is present in N. and the latter in R. McCarrison has also noted enuresis. Its presence is probably related to the frequency. The origin of these symptoms may be in the hypothalamic regions of the brain. We would attribute them to a fairly extensive involvement of the central gray matter. They occur in epidemic encephalitis as well.

Hyperaffectivity. The functional element was considered of great, if not sole importance in the genesis of the stuttering and choreiform movements by others who first observed R. An attempt at reeducation and a brief course of psychoanalysis have left R. worse than before.

Surely, the foot deformities, constipation, enuresis and Babinski sign are not to be considered of functional origin.

Pathologic Anatomy. (*a*) From the clinical findings, we may presume that the cerebral cortex in some part is affected. The disorders of neuromuscular control, chorea, athetosis, static fits, rigidity and ataxia suggest involvement of the basal ganglions and perhaps the cerebellum. Nystagmus and stuttering are no doubt infracortical in origin. The enuresis and constipation may also be due to disease of the central ganglions (namely, central origins of the visceral nervous system). (*b*) Weygandt[20] noted degenerative lesions of the nerve cells, leptomeningitis and perivascular leukocytic

infiltration, but he did not consider these specific. In three cases of hypothyrodism with mental disorders, Brun and Mott,[21] and Mott,[22] found generalized chromatolysis in the entire nervous system. This chromatolysis did not spare any special group of cells; however, the autonomic bulbar nuclei (vago-glossopharyngeal), the cerebrospinal motor neurones and the sympathetic system were especially involved.

Both these authors and Weygandt found vacuolization of nerve cells, globular and "rapetissées" forms, excentricity of nuclei, as well as slight changes in the fibrils of the small pyramidal cells and those of Betz.

Marie, Trétiakoff and Stumfer[23] found marked deposits of iron and very little calcium in the walls of the bloodvessels of the cerebellum and striatum, especially in the globus pallidus. Intimal thickening was present, and even produced an obliterating endarteritis. As they state, their material was not very well fixed and could not be used for finer staining. The very small amount of calcium and large amount of iron in a woman of thirty-six does not suggest arteriosclerosis at all. Since iron is concerned in oxidation processes, these authors suggest that the lowered oxidation rate of hypothyroidism may have caused this deposit of iron.

Edmunds[24] found profound changes in the cells of the spinal cord, medulla, cerebellum (Purkinje cells) and cortex (medium and large pyramidal cells) with chromatolysis to total destruction, in thyreoparathyroidectomized dogs and cats. The calcium of the brain was one-half normal. Eaves and Croll[11] in the case above mentioned, found chromatolysis of nerve cells and accumulation of fatty granules in most regions, especially marked in the sympathetic ganglia. There was complete chromatolysis in the cerebral cortex, and the pyramidal tracts were so poorly myelinated as to suggest the fetal status, although the patient was fourteen years of age. Dye[25] examined the brains of thyroidectomized animals and found cell changes which were not specific. The "chromatolysis" was also found in tetany and fatigue states.

Treatment. This depends upon thyroid gland administration and general nourishment. In infants, the quantity of the mother's milk should be watched as well as her condition in regard to thyroid secretion. Beyond this, an attempt should be made to eliminate intestinal parasites and any chronic infection.

Conclusions. The condition may be defined as thyroneural dystrophy. It is a familial and probably congenital disorder of neuromuscular control of central origin, consisting of any or all of the following: chorea, athetosis, static fits, rigidity, ataxia, abnormal reflex changes, postural defects, and signs referable to disturbed function of the vegetative nervous system associated with a variable degree of mental and thyroid defect. The condition may be so

severe as to imitate precisely advanced cases of cerebral diplegia. Nystagmus, squint and stuttering may be present.

No specific pathology is known beyond changes in the internal structure of the cells of the nervous system and a deposit of calcium and iron about the bloodvessels.

It seems probable to us that there is a common but unknown cause of both the thyroid and neural dystrophy. It is well-known that a normal thyroid gland is necessary for the development of a normal central nervous system; hence, when thyroid gland is administered early in cases of thyroneural dystrophy, the disorders due to the thyroid defect during growth may disappear. In this type of case, thyroid-gland administration is apt to be most beneficial.

Reference is made to the possibility of a superimposed toxi-infectious neural involvement due to the letting down of the blood—cerebrospinal fluid barrier for colloids, in consequence of the thyroid insufficiency. Such an hypothesis may explain the late appearance of the nervous symptoms and the ineffectiveness of thyroid therapy.

BIBLIOGRAPHY.

1. McCarrison, R.: Observations on Endemic Cretinism in the Chitral and Gilgit Valleys, Proc. Roy. Soc. Med., Sect. Med., 1908, **2**, 1.

2. Crookshank, F. G.: A Case of Nervous Cretinism, Proc. Roy. Soc. Med., Sect. Dis. Child., 1913, **7**, 26.

3. Langmead, F.: Nervous Cretinism, Proc. Roy. Soc. Med., Sect. Dis. Child., 1913, **6**, 149.

4. Manson, L. S.: Unusual Manifestations in Cretinism, Med. Rec., 1910, **77**, 7.

5. Söderbergh, G.: Faut-il attribuer à une perturbation des fonctions cérébelleuses certains troubles moteurs du myxoedème, Rev. neurol., 1910, **18**, 487.

6. Vetlesen, H. L.: Paralysis Agitans und Myxödem, Ztschr. f. d. ges. Neurol., 1914, **26**, 462.

7. Barkman, A.: Ein Fall von Myxödem mit Symptomen von Zentralen Nervensystem, Deutsch. Ztschr. f. Nervenh., 1923, **78**, 293.

8. Quervain, F. de: Cretinisme, états hypothyroidiens et système nerveux, Schweiz. Arch. f. Neurol. u. Psychiat., 1924, **14**, 3.

9. Lundberg, R.: Deux cas de myxoedème s'accompagnant de symptômes localisables dans le système nerveux central, Acta med. Scandinav., 1924, **61**, 240.

10. Lundberg, R.: Cinq cas de myxoedème s'accompagnant de symptômes localisables dans le système nerveux central, Acta med. Scandinav., 1926, Suppl. Vol., **16**, 182.

11. Eaves, E. C., and Croll, M. M.: A Case of Nervous Cretinism with Histologic Examination of the Organs, J. Path. and Bacteriol., 1928, **31**, 163.

12. Naville, F.: Les diplegies congénitales et les troubles dysthyroidiens dans les classes d'énfants anormaux de Genève, Étude clinique et statistique, Schweiz. Arch. f. Neurol. u. Psychiat., 1923, **13**, 559.

13. Barlow, R. A.: The Study of Vestibular Nerve Function in Myxedema, Am. J. Med. Sci., 1922, **164**, 401.

14. Chagas, C.: Les formes nerveuses d'une nouvelle trypanosomiase, Nouv. iconogr. de la Salpétrière, 1913, **26**, 1.

15. Walter, F. K.: Uber die Bedeutung der Schildrüse für das Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat., 1911, **4**, 67.

16. Stern, L., Rapoport, J., Kremlew, L.: Effet de la Thyroïdectomie et de la Castration sur le Fonctionnement de la Barrière Hémato-encéphalique, Compt. rend. des Séances et mém. de la Soc. de biol., 1927, **97**, 644.

17. Hunt, J. R.: On the Occurrence of Static Seizures in Epilepsy, Arch. Neurol. and Psychiat., 1922, **8**, 315.

18. Kraus, W. M., and Goodhart, S. P.: On the Deformity of the Foot in Dystonia Musculorum, Arch. Neurol. and Psychiat., 1924, **11**, 436.
19. Kraus, W. M., and Rabiner, A. M.: On the Production of Neuromuscular Patterns by Release of Spinal Integration after Decerebration, J. Neurol. and Psychopath., 1922, **3**, 209.
20. Weygandt, W.: Ueber Hirnrindveränderung bei Mongolismus, Kretinismus und Myxödem, Ztschr. f. d. Erf. u. Beh. des jug. Schwachsinns., 1912, **5**, 428.
21. Brun, R., and Mott, F. W.: Microscopic Study of the Nervous System in Three Cases of Spontaneous Myxedema, Proc. Roy. Soc. Med., Sect. Psychiat., 1912–1913, **6**, 75.
22. Mott, F. W.: Microscopic Examination of the Central Nervous System in Three Cases of Spontaneous Hypothyroidism in Relation to a Type of Insanity, Proc. Roy. Soc. Med., Sect. Psychiat., 1915, **8**, 58.
23. Marie, P., Trétiakoff, C., and Stumfer, E.: Étude anatomo-pathologique des centres nerveux dans un cas de myxoedème congénital avec crétinisme, l'Encéphale, 1920, **11**, 601.
24. Edmunds, W.: The Changes in the Central Nervous System Resulting from Thyroparathyroidectomy, Proc. Roy. Soc. Med., Sect. Neurol., 1912, **5**, 179.
25. Dye, J. A.: Comparable Cell Changes in the Central Nervous System in Cretinism, Parathyroid Tetany and Fatigue, Proc. Soc. Exp. Biol. and Med., 1925, **23**, 119.

THE INTRAVENOUS USE OF GELATIN SOLUTION IN HEMORRHAGE.

(An Experimental Study.)

By William L. Wolfson, M.D., F.A.C.S.,
ATTENDING SURGEON UNITED ISRAEL ZION HOSPITAL.
AND
Frank Teller, B.S., M.D.,
ASSISTANT ATTENDING SURGEON UNITED ISRAEL ZION HOSPITAL.

(From the Department of Pathology, United Israel Zion Hospital, Brooklyn, N. Y.)
(Max A. Goldzieher, M.D., Director of Laboratories.)

Low blood pressure due to hemorrhage is most adequately controlled by the direct transfusion of whole blood. There are occasions of sudden severe bleeding in surgical practice that demand immediate combative treatment with a substitute intravenous solution, available and efficient to elevate the blood pressure. The solutions commonly favored are saline, glucose and gum acacia. It is a frequent observation that these solutions have not proven altogether satisfactory, mainly because of their failure to sustain a high blood-pressure level over a prolonged period of time.

With the object of finding a colloid solution that will both elevate and maintain the blood pressure after hemorrhage, a series of experiments on rabbits was conducted with the results herewith presented.

Procedure. The technique employed was the same throughout all the experiments. Healthy rabbits of about 2 to 2½ kg. were anesthetized. The animals were bled from the right femoral artery by

introducing a cannula connected with an aspirating syringe, and the blood withdrawn in definite amounts necessary to produce a decreased blood pressure. The solution under study was then slowly injected into the right internal jugular vein. The blood pressure tracings were recorded on an electrokymograph by introducing into the right carotid artery, a cannula connected with a rubber tube attached to a mercury manometer.

The refractive index and a red blood-cell count were determined before and after each blood letting.

Preparation of Stock Solution of Gelatin. Fifty grams of "Difco" gelatin, 1 gm. of sodium carbonate and 0.9 gm. of sodium chlorid were placed in a flask containing 400 cc. of distilled water and boiled for fifteen minutes.* This solution was filtered through glass wool and autoclaved for one hour at 252.2° F.; then permitted to cool and solidify. For use the gelatin in the flask was warmed, to which was then added 600 cc. of sterile distilled water, and the whole heated to a temperature of 98.6° F.

This stock solution was cultured for bacterial growth under aërobic and anaërobic conditions. Tests for toxicity were made by injecting 10 cc. of this solution into the veins of rabbits for six consecutive days. Though the animals were carefully watched for any untoward symptoms, there was no evidence of intravascular clotting or other ill effects, for these animals were subjected to further experiments and the organs, when examined after death, were found to be normal. Bayliss,[1] in "Intravenous Injection in Wound Shock" says that an unwelcome property of gelatin is that of causing intravascular clotting. No intravascular clotting was obtained with our stock gelatin solution.

The results were compared with other solutions, namely: 0.9 per cent saline, 5 per cent dextrin, 5 per cent starch and 2½ per cent gelatin.

Experiment 1.—0.9 Per Cent Normal Saline Solution—Refractive Index 1.3340. From a normal rabbit weighing 2 kg., with a blood pressure of 90 mm.Hg., a refractive index of 1.3480, 28 cc. of blood was removed. The pressure dropped to 40 mm.Hg., where it remained.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	90	4,700,000	1.3480
On withdrawal of 28 cc. blood	40	2,600,000	1.3480
Two minutes after injection of 25 cc. normal saline	58	2,600,000	1.3480
Ten minutes after injection of 25 cc. normal saline	40	2,610,000	1.3480
Five minutes after injection of 20 cc. 5 per cent gelatin	85	2,608,000	1.3440
One hour after injection of 50 per cent gelatin	80	2,610,000	1.3450

* The gelatin is heated in the presence of sodium chlorid and sodium carbonate to prevent decomposition, loss of viscosity and hemolysis of red cells.

Two minutes after the injection into the right internal jugular vein of 25 cc. of normal saline solution, the blood pressure rose to 58 mm.Hg., where it remained ten minutes before dropping to 40 mm.Hg.

Twenty cubic centimeters of 5 per cent gelatin solution was then injected intravenously. The blood pressure mounted to 85 mm.Hg., retaining for several hours a level of 80 mm.Hg.

Experiment 2.—5 Per Cent Dextrin—Refractive Index 1.3420. From a healthy rabbit weighing 2 kg., with a blood pressure of 90 mm.Hg., a red cell count of 5,400,000 per c.mm. and a refractive index of 1.3480, 30 cc. of blood was removed and the blood pressure dropped to 45 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	90	5,400,000	1.3480
On withdrawal of 30 cc. blood	45	2,800,000	1.3480
Five minutes after injection of 30 cc. 5 per cent dextrin	65	2,810,000	1.3450
Sixty minutes after injection of 5 per cent dextrin	65	2,806,000	1.3450
Ninety minutes after injection of 5 per cent dextrin	65	2,816,000	1.3480
Three hours after injection of 5 per cent dextrin	40	2,820,000	1.3480

Thirty cubic centimeters of warm 5 per cent dextrin solution was immediately injected. The blood pressure rose to 65 mm.Hg., and the refractive index registered 1.3450, remaining the same at the end of an hour.

Ninety minutes after the injection, however, the refractive index of the blood was back to normal while the blood pressure still registered 65 mm.Hg. Three hours later the animal died.

Experiment 3.—5 Per Cent Starch Solution—Refractive Index 1.3390. From a rabbit weighing 2.5 kg., with a blood pressure of 110 mm.Hg. and a refractive index of 1.3456, there were withdrawn 18 cc., 17 cc. and 15 cc. of blood, making in all a total of 50 cc., reducing the blood pressure to 50 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	110	4,960,000	1.3456
On withdrawal of 18 cc. blood	70	4,100,000	1.3456
On withdrawal of 17 cc. blood	65	3,800,000	1.3456
On withdrawal of 15 cc. blood	50	2,900,000	1.3456
Five minutes after injection of 30 cc. 5 per cent starch solution	80–85	2,910,000	1.3410
Sixty minutes after injection of 30 cc. 5 per cent starch solution	30–35	2,900,000	1.3430

Thirty cubic centimeters, of warm 5 per cent starch solution was slowly injected, sending the blood pressure immediately up to 80 to 85 mm.Hg. Twenty-five minutes later it had fallen to 35 mm.Hg.

Twenty-five cubic centimeters of warm 5 per cent starch solution was again injected intravenously, with no resulting rise in blood pressure. The animal died one hour later.

Experiment 4.—2.5 Per Cent Gelatin Solution—Refractive Index 1.3360. From a rabbit weighing 2.5 kg., with a blood pressure of 110 mm.Hg. and a refractive index of 1.3480, 40 cc. of blood was withdrawn, reducing the blood pressure to 48 mm.Hg.

Upon the injection of 40 cc. of warm 2.5 per cent gelatin solution, the blood pressure rose to 105 mm.Hg., where it remained for thirty-two minutes and then gradually declined to 60 mm.Hg.

Another injection of 20 cc. of 2.5 per cent gelatin solution elevated the blood pressure to 85 mm.Hg., where it remained for twenty minutes before it gradually fell. The animal died one hour and thirty-five minutes later.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	110	5,400,000	1.3480
Five minutes after withdrawal of 40 cc. blood	48	2,000,000	1.3480
Four minutes after injection of 40 cc. 2.5 per cent gelatin	105	2,100,000	1.3420
Thirty-two minutes after injection of 40 cc. 2.5 per cent gelatin	60	2,100,000	1.3445
Five minutes after second injection of 20 cc. 2.5 per cent gelatin	85	2,000,000	1.3420
Thirty minutes after injection of 20 cc. 2.5 per cent gelatin solution	70	2,000,000	1.3440
Eighty minutes after injection of 20 cc. 2.5 per cent gelatin solution	45	2,000,000	1.3470

Experiment 5.—2.5 Per Cent Gelatin Solution—Refractive Index 1.3360. From a normal rabbit weighing 2 kg., with a blood pressure of 75 mm.Hg. and a refractive index of 1.3480, 30 cc. of blood was withdrawn, reducing the blood pressure to 40 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	75	5,200,000	1.3480
Four minutes after withdrawal of 30 cc. blood	40	3,710,000	1.3480
Five minutes after injection of 25 cc. 2.5 per cent gelatin solution	45	3,520,000	1.3420
Twenty minutes after injection of 25 cc. 2.5 per cent gelatin solution	30	3,550,000	1.3440
Second injection of 20 cc. 2.5 per cent gelatin solution	40	....	1.3420
Thirty minutes after injection of 20 cc. 2.5 per cent gelatin solution	40	3,540,000	1.3475

On the slow injection of 25 cc. of warm 2.5 per cent gelatin solution into the right internal jugular vein, the blood pressure rose but 5 mm.Hg., and in the space of twenty minutes receded to 30 mm.Hg.

Again 20 cc. of 2.5 per cent gelatin solution was injected, followed by an immediate rise of blood pressure to 50 mm.Hg., which lasted thirty minutes before a gradual decline.

Experiment 6.—5 Per Cent Gelatin Solution—Refractive Index 1.3420. From a rabbit weighing 2 kg., with a blood pressure of 95 mm.Hg. and a refractive index 1.3475, 30 cc. of blood was taken, reducing the blood pressure to 45 mm.Hg.

An immediate injection of 35 cc. of 5 per cent gelatin solution elevated the blood pressure to 90 mm.Hg. One-half hour later the pressure was 85 mm.Hg., ranging between 80 and 85 for the next five hours.

	Blood pressure, mm.Hg.	Red blood cells, per cmm.	Refractive index.
Normal	95	5,100,000	1.3475
Seven minutes after withdrawal of 30 cc. blood	45	2,260,000	1.3475
Seven minutes after injection of 35 cc. 5 per cent gelatin	90	2,270,000	1.3445
Thirty minutes after injection of 35 cc. 5 per cent gelatin	85	2,250,000	1.3448
One hour after injection of 35 cc. 5 per cent gelatin	85	2,260,000	1.3450
Two hours after injection of 35 cc. 5 per cent gelatin	80	2,262,000	1.3456
Four hours after injection of 35 cc. 5 per cent gelatin	85	2,266,000	1.3468
Five hours after injection of 35 cc. 5 per cent gelatin	80	2,268,000	1.3470

Experiment 7.—5 Per Cent Gelatin Solution—Refractive Index 1.3420. From a normal rabbit weighing 2 kg., with a blood pressure of 70 mm.Hg. and a refractive index of 1.3478, 20 cc. of blood was removed. The blood pressure fell to 50 mm.Hg. and remained at this level.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	70	5,400,000	1.3478
Seven minutes after withdrawal of 20 cc. blood	50	4,100,000	1.3478
Seven minutes after withdrawal of 30 cc. blood	35	2,340,000	1.3478
Seven minutes after injection of 32 cc. 5 per cent gelatin	65	2,340,000	1.3445
Eighty-five minutes after injection of 32 cc. 5 per cent gelatin	65	2,360,000	1.3450
Four hours after injection of 32 cc. 5 per cent gelatin	65	2,300,000	1.3448
Five hours after injection of 32 cc. 5 per cent gelatin	65	2,660,000	1.3450
Eight hours after injection of 322 cc. 5 per cent gelatin	70	2,586,000	1.3470

Upon further removal of 30 cc. of blood, the pressure dropped to 35 mm.Hg.

Thirty-two cubic centimeters of warm 5 per cent gelatin solution was then slowly injected intravenously, sending the blood pressure immediately up to 65 mm.Hg., where it remained for at least eight hours.

Experiment 8.—5 Per Cent Gelatin Solution—Refractive Index 1.3420. From a normal rabbit weighing 2.5 kg., with a blood pressure of 130 mm.Hg. and a refractive index of 1.3470, 18 cc. of blood was withdrawn, the pressure falling to 90 mm.Hg. Again there was removed 10 cc. of blood, the pressure dropping further to 75 mm.Hg. Another withdrawal of 10 cc. of blood reduced the pressure to 70 mm.Hg. Thus a total of 38 cc. of blood was removed in a very short space of time.

Thirty-five cubic centimeters of warm 5 per cent gelatin solution was then injected, sending the blood pressure up to 140 mm.Hg. Five minutes later, the refractive index of the circulating blood was found to be 1.3440.

The blood pressure, the red blood-cell count and the refractive index of the blood were recorded at intervals of one, three and six hours as indicated on the chart. The gelatin solution apparently remained in circulation for about 6 hours.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	130	4,680,000	1.3470
Two minutes after withdrawal of 18 cc. blood	90	4,000,000	1.3470
Two minutes after withdrawal of 10 cc. blood	75	3,200,000	1.3470
Two minutes after withdrawal of second 10 cc. blood	70	2,800,000	1.3470
Five minutes after injection of 35 cc. 5 per cent gelatin	140	2,800,000	1.3440
Sixty minutes after injection of 35 cc. 5 per cent gelatin	140	2,780,000	1.3440
Three hours after injection of 35 cc. 5 per cent gelatin	135	2,810,000	1.3450
Six hours after injection of 35 cc. 5 per cent gelatin	130	2,920,000	1.3460

Discussion. The recorded experiments on blood pressure point to a marked difference between the effects of saline, dextrin, starch and gelatin solutions injected intravenously in animals after bleeding.

With saline infusion there was a fairly rapid elevation of blood pressure, maintained for only a short time however, and which never approached the original figure. The refractive index of the serum did not change in our experiment, seeming to indicate a rapid elimination of the injected fluid.

In the experiments with dextrin solution, we obtained a rapid response. The blood pressure rose immediately after the injection

from a 45 to a 65 mm.Hg. reading, but it was not maintained for any length of time. The elimination of the dextrin solution appears to have set in after one hour, as indicated by the rise in the refractive index.

Starch solution produces a quicker reaction than dextrin, but is followed by a more rapid decline. The early elimination of the starch is indicated by the rise in the refractive index, occurring within one hour.

In our first experiments with gelatin we used a 2.5 per cent solution as advocated by Hogan,[2] but failed to obtain prolonged elevated blood pressure. Bayliss gives the probable cause for this failure and states that 6 per cent gelatin gives permanent results.

As demonstrated by further experiments, the use of a 5 per cent gelatin solution showed that not only can the blood pressure be restored to the original height and above it, but that it can be maintained at that level for many hours. That this is due to the persistence of the gelatin solution in the circulating blood is borne out by the change in the refractive index, which in our experiments decreased after the injection of gelatin, and remained at that lower level for several hours. Since the rise of the refractive index was not concomitant with a drop in the blood pressure, it is possible that the gelatin still remained in the circulation.

Our experiments have impressed us with the favorable effect of the injection into the blood stream of a 5 per cent gelatin solution.

Conclusion. Intravenous injection of 5 per cent gelatin solution into animals with low blood pressure due to hemorrhage restores the blood pressure for several hours. The continued presence in the circulation of the gelatin solution is indicated by the low figure reached and maintained by the refractive index. Solutions of weaker concentration are not as effective.

No untoward effects of gelatin were demonstrated in the animals under experiment.

Solutions of saline, dextrin and starch elevate the blood pressure, but fail to maintain the elevated level. The rapid elimination of these solutions is indicated by the quick return of the refractive index to normal.

REFERENCES.

1. Bayliss, W.: Intravenous Injection in Wound Shock, 1918.
2. Hogan: J. Am. Med. Assn., 1915, **64**, 721.

REVIEWS.

PUBLIC HEALTH AND HYGIENE: IN CONTRIBUTIONS BY EMINENT AUTHORITIES. Edited by WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City. Second edition, thoroughly revised. Pp. 902; 123 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $9.00.

PREVENTIVE medicine has experienced remarkable advances in recent years, both in theory and application. Moreover, the "growing opinion that public health is to a large extent purchasable by effort and money, and that it is worth purchasing, has stimulated health authorities to develop their opportunities and to assume greater responsibilities." The new edition of Dr. Park's work, thoroughly revised and with new chapters on cancer control and on aseptic technique in the control of communicable diseases, covers well the great strides forward in our knowledge concerning hygiene and in the increasing scope of public health work. Twenty-four eminent authorities have contributed to make this a truly authoritative volume. The material is presented in a thoroughly practical manner, with thought particularly for medical officers, physicians and medical students. The Reviewer was impressed by the very small amount of reduplication of subject matter in chapters on closely related topics, although written by different men.

R. K.

THE LIFE OF HERMANN M. BIGGS, M.D., D.SC., LL.D., PHYSICIAN AND STATESMAN OF THE PUBLIC HEALTH. By C.-E. A. WINSLOW, DR. P.H., Professor of Public Health, Yale School of Medicine. Pp. 432; 35 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $5.00.

THOUGH many doubtless know of Hermann Biggs as an important factor for many years in the New York City Department of Health, probably few would rank him—as the London School of Hygiene and Tropical Medicine have publicly done—as one of the twenty-one who have done most to advance public health since the seventeenth

century. The reasons for such a choice become apparent on reading Doctor Winslow's sympathetically and pleasantly written narrative. More than a biography of a distinguished sanitarian, the book serves as a typical story of the development of modern public health. The accounts of the administrative control of tuberculosis, the spreading of diphtheria antitoxin, the combatting of other preventable diseases, in fact the demonstration that "health was purchasable," alternate with fascinating glimpses of an interesting and versatile personality that should recommend the book to all concerned with the health of the public. E. K.

MANUAL OF PROCTOLOGY. By T. CHITTENDEN HILL, PH.B., M.D., F.A.C.S., Instructor in Proctology, Harvard. Graduate School of Medicine. Third edition. Pp. 272; 86 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $3.50.

THE previous (second) edition of this useful and practical manual was reviewed in these columns three years ago. The present edition is practically identical with the former with the exception of the final chapter, which deals with cancer of the rectum. This has been written by Dr. E. Parker Hayden and is largely devoted to a description of the well-known Jones operation. R. G.

AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS. By VARIOUS WRITERS. Edited by HERBERT FRENCH, C.B.E. (MILIT.), M.D., (OXON.), F.R.C.P. (LOND.), Physician to H. M. Household; Physician and Lecturer, Guy's Hospital; Consulting Physician to Queen Alexandra's Military Hospital, Milbank. Fourth edition. Pp. 1171; 701 illustrations (179 in colors). New York: William Wood & Co., 1928. Price, $18.00.

THIS work needs no introduction to the medical public. Three previous editions and seven reprintings, as well as translations into Spanish and Italian, are sufficient evidence of its popularity. It is with delight, therefore, that we welcome the new fourth edition of the book after its being five years out of print. Written by twenty contributors, it is a treatise on the application of differential diagnosis to all the main signs and symptoms of disease, and covers the whole ground of medicine, surgery, gynecology, ophthalmology, dermatology and neurology. As in previous editions, the material is presented by articles on signs and symptoms, alphabetically arranged, with a discussion of the methods of distinguishing between

the various diseases in which each symptom may occur. A most valuable feature is an index of amazing completeness—225 pages with more than 90,000 page references—in which the symptoms, in addition to being singly listed, are gathered together under the headings of the various diseases. The proper use of the book, therefore, requires careful reference to the index as well as to the text. The illustrations are numerous and well done. All physicians will find in this volume a most satisfactory and valuable diagnostic aid. R. K.

DIABETES LATENTE. By DR. FELIX PUCHULU. Pp. 213. Buenos Aires: Talleres Gráficos Ferrari Hnos., 1929.

LATENT diabetes is here considered as preceding and separate from early diabetes; sugar tolerance is lowered, but glycosuria does not follow ingestion of carbohydrates. Demonstration of this state, perhaps together with some of the clinical symptoms, permits a diagnosis and installation of dietetic treatment similar to that of mild diabetes. Illustrative cases are given. E. K.

A HISTORY OF THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By P. M. ASHBURN, Colonel, Medical Corps, U. S. Army. Pp. 448. Boston and New York: Houghton Mifflin Company, 1929.

"THE Medical Department of the United States Army has an enviable record which is little known to the general public. It has to its credit the conquest of yellow fever the elucidation of the process of gastric digestion, a prominent share in the reduction of communicable diseases, and many other notable achievements.

"This lucid, simple, unbiased account of its history deals not only with the story of the Medical Department from Revolutionary days to the present hour, but also with the general status of the Army as a whole and the condition of medicine in each period. No work like it has heretofore appeared."

This quotation on the paper cover of the book well indicates its scope and nature. As General Ireland states in his introduction, it is an interesting, true story, "documented and accurate, but not long drawn out or hard to read." Even the work of Reed, Gorgas and the Department in general during the World War is not sufficiently known by the medical and general public, still less is that of Senter of Quebec fame, Lovell in 1812, Beaumont and St. Martin, Billings and other officers of the department, who made valuable contributions to varied aspects of medical progress. E. K.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 226; 61 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $7.50.

IN spite of the numerous books on electrocardiography that have recently appeared, chiefly dealing to be sure with clinical aspects, the author feels that there is still "need of a simple yet comprehensive treatise by an author who can reasonably lay claim to experience." Certainly Dr. Wiggers fulfills the latter requirement, and it may also safely be said that his book makes as good a presentation as can be found today of such matters as apparatus, technique, fundamental physical and physiological principles, etc. Slightly less than half the book is devoted to clinical interpretations and diagnosis. This is accurately written and sufficiently illustrated, though it may not be quite as useful for the clinical beginner as some of the more elaborately detailed works above referred to.

E. K.

NOTES ON CHRONIC OTORRHEA, WITH SPECIAL REFERENCE TO THE USE OF ZINC IONIZATION IN THE TREATMENT OF SELECTED CASES. By A. R. FRIEL, M.A., M.D. (UNIV. DUB.), F.R.C.S.I., Assistant Aurist, School Medical Service, London County Council; Aurist to Tottenham, Hornsey, and Walthamstow Education Committees. Pp. 87; 54 illustrations. New York: William Wood & Co., 1929. Price, $2.25.

THE subject and method of zinc ionization treatment for otorrhea is one with which every otologist should be familiar. Simple fundamental experiments followed by methods of clinical application, together with charted results by various experienced observers, emphasizes the importance, if not actual necessity in many cases, for this specialized treatment. Emphasis is placed on accurate diagnosis, proper classification of type of suppuration, barriers encountered and instruments demanded to meet the individual requirements. It is far in advance of the medicated "ear drops" method which has held sway for so many years.

D. H.

DISEASES OF THE LIVER, GALL BLADDER AND BILE DUCTS. By SIR HUMPHREY ROLLESTON, BART, K.C.B., and J. W. MCNEE. Third edition. New York: Macmillan Company, 1929.

THE review of the first edition of this work was written for this journal by Sir William Osler (May, 1905) and signed with the

initials E. Y. D., well known to the initiated. The opinion expressed then of the usefulness and value of the book has been thoroughly established. In this edition Sir Humphrey Rolleston has associated Dr. J. W. McNee, whose work on jaundice is well known. It may be said that this work is to be regarded as the best which we have on the subjects with which it deals and it is a storehouse of facts and references. The advances in our knowledge of hepatic and biliary disorders since the previous edition have been many, especially relating to jaundice, functional tests of hepatic disease and cholecystography. The discussion on cirrhosis has always seemed to the Reviewer to be especially clear. Throughout the book the orderly arrangement is a great aid to the reader. Altogether this work can be commended as the best discussion of the subject and one to which every student of hepatic and biliary disease must refer. T. M.

THE NEUROSES. By ISRAEL WECHSLER, M.D., Associate Professor of Clinical Neurology; Attending Neurologist to the Neurological Institute, The Montefiore and Sydenham Hospitals, New York City. Pp. 330. Philadelphia: W. B. Saunders Company, 1929. Price, $4.00.

THIS is an expansion of a chapter from a larger work. The entire approach and classification is Freudian and bears the stamp of approval of the founder of that School. Psychasthenia is not grouped as such and epilepsy is not included. Thirty-two case reports illustrate, well, the author's viewpoint. Drugs are not ignored but one should not speak of luminal as a "mild hypnotic."

The value of *rest cures* are quite accurately gauged by their employment in exhausted, anemic and emaciated patients, while their usefulness is not seen in "neuroses rooted in mental conflicts over inner and outer situations."

An excellent addition to psychoanalytic literature. N. Y.

OSTEOMYELITIS AND COMPOUND FRACTURES. By H. WINNETT ORR, F.A.C.S., Chief Surgeon of the Nebraska Orthopedic Hospital. Pp. 208; 54 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $5.00.

THIS book is a presentation of the Orr method of treatment of infected wounds of the bones and joints which, in brief, consists of the free opening and removal of dead tissue, open drainage by sterile vaseline pack, maintenance of rest by the application of an extensive plaster-of-Paris cast, and omission of dressings for a matter of several weeks.

The clinical results obtained by the author and other surgeons in the west are remarkable and if like results are obtained generally, it will mean a decided advance in this field. The surgeons in the east who are now using this method are enthusiastic.

The book is written in a pleasing style, is well illustrated and worth owning. J. M.

TUMORES PRIMITIVOS DE LA PLEURA. By DR. JOSE W. TOBIAS. Pp. 479; 60 illustrations. Buenos Aires: El Ateneo, 1928.

THOUGH the book is divided into four parts (I, Endothelioma; II, tumors, malignant, benign and mixed; III, inflammatory tumors; IV, cystic tumors), the discussion of the first is much the most voluminous and profitable. The author believes that there is a true primary endothelioma of the pleura of connective-tissue origin, and that though bronchial carcinomata may closely simulate it, they can always be differentiated microscopically. Symptomatology, diagnosis and treatment are suitably discussed. Adenoma lipoma, chondroma, fibroma, mixed tumors, hydatid and dermoid cysts, tuberculosis, syphilis and actinomycosis receive more superficial treatment. E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Œsophageal Obstruction.** By A. LAWRENCE ABEL, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 234; 132 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $9.00.

Annals of the Pickett-Thomson Research Laboratory. Volume IV. November, 1928, Part I and April, 1929, Part II. The Pathogenic Streptococci. An Historical Survey of their Rôle in Human and Animal Disease.* Pp. 494; 18 illustrations. London: Baillière, Tindall & Cox, 1929.

*The Cytoarchitectonics of the Human Cerebral Cortex.** By CONSTANTIN VON ECONOMO. Translated by DR. S. PARKER. Pp. 186; 61 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $6.25.

*Diagnosis and Treatment of Deformities in Infancy and Early Childhood.** By M. F. FORRESTER-BROWN, M.S., M.D. (LOND.). Pp. 199; 79 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $4.15.

*The Robert Jones Birthday Volume. A Collection of Surgical Essays.** Pp. 434; illustrated. New York: Oxford University Press, American Branch, 1929. Price, $13.00.

*The Autonomic Nervous System.** By ALBERT KUNTZ, PH.D., M.D. Pp. 576; 70 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $7.00.

* Reviews of titles followed by an asterisk will appear in a later number.

*Laboratory Manual of the Division of Bacteriology, Peking Union Medical College.** Prepared under direction of C. E. LIM. Pp. 154. Peking, China: Peking Union Medical College Press, 1929. Price, $1.50.

Medical Clinics of North America, Boston Number, July, 1929, Volume XIII, No. 1. Pp. 280; 36 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*Mechano-Therapy.** By MARY REES MULLINER, M.D. Pp. 265; 57 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $2.75.

Progressive Medicine, Volume XI, June, 1929. Pp. 389; illustrated. Philadelphia: Lea & Febiger, 1929.

Surgical Clinics of North America (Mayo Clinic Number), August, 1929. Pp. 208; 72 illustrations. Philadelphia: W. B. Saunders Company, 1929.

NEW EDITIONS.

Diseases of the Larynx. By HAROLD BARWELL, M.B. (LOND.) F.R.C.S. (ENG.). Third edition. Pp. 278; 112 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.65.

Bodily Changes in Pain, Hunger, Fear and Rage. By WALTER B. CANNON, M.D., Sc.D., LL.D. Second edition. Pp. 404; 43 illustrations. New York: D. Appleton & Co., 1929. Price, $3.00.

American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, M.D. Fifteenth edition. Pp. 1427; 525 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, plain, $7.00; Thumb index, $7.50.

Herman's Difficult Labor. Revised by CARLTON OLDFIELD, M.D. (LOND.), F.R.C.S. Seventh edition. Pp. 560; 105 illustrations. New York: William Wood & Co., 1929. Price, $5.50.

Artificial Sunlight and its Therapeutic Uses. By FRANCIS HOWARD HUMPHRIS, M.D. (BRUX.), F.R.C.P. (EDIN.), M.R.C.S. (ENG.). Fifth edition. Pp. 340; 31 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.25.

Ker's Infectious Diseases. Revised by CLAUDE RUNDLE, O.B.E., M.D. (LOND.), M.R.C.S. (ENG.). Third edition. Pp. 614; 67 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $10.50.

Hemorrhoids. By ARTHUR S. MORLEY, F.R.C.S. (ENG.). Pp. 122; 10 illustrations. Fourth impression revised and enlarged. New York: Oxford University Press, American Branch, 1929. Price, $2.00.

The Treatment of Fractures and Dislocations in General Practice. By C. MAX PAGE, D.S.O., M.S. (LOND.), F.R.C.S. and W. ROWLEY BRISTOW, M.B., B.S. (LOND.), F.R.C.S. Third edition. Pp. 284; 161 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $4.25.

Tuberculosis. Its Prevention and Home Treatment. By H. HYSLOP THOMSON, M.D., D.P.H. Third edition. Pp. 99. New York: Oxford University Press, American Branch, 1929. Price, $0.75.

The Principles of Electrotherapy and their Practical Application. By W. J. TURRELL, M.A., D.M., B.CH. (OXON.). Second edition. Pp. 413; 34 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $4.75.

Tweedy's Practical Obstetrics. Edited and largely rewritten by BETHEL SOLOMONS, M.D., F.R.C.P.I. Sixth edition. Pp. 759; 294 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $7.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

An Investigation of Various Factors which Affect the Sedimentation Rate of the Red Blood Cells.—Probably because of the ease in which the test may be carried out rather than from any definite information which is given to the clinician, a very extensive bibliography on the sedimentation rate of the red blood cells in different types of disease has resulted. Two papers that have been recently published are of some interest in this connection. The first of these is by ROURKE and PLASS (*J. Clin. Invest.*, 1929, **7**, 365). They studied various factors which may influence the sedimentation rate of the erythrocytes. These authors found that heparin is the ideal anticoagulant. The blood, if it stands longer than six to twelve hours, leads to a slowing of the rate, and rapid centrifuging of the blood does not affect its settling speed even after remixing. Blood dilution leads to a rapid settling of the cells. Aëration of venous blood does not seem to affect the rate of settling so that collection of blood under oil is not necessary. Increased changes in temperature make for more rapid sedimentation, but not within the range of ordinary room temperature. Ingestion of food seems to have slight, if any, effect, and the same statement applies to short, violent exercise.

Sedimentation Rate of Red Blood Corpuscles in Acute and Chronic Infections.—WYLIE (*J. Infect. Dis.*, 1929, **45**, 6) followed the method of Zeckwer and Goodell. She found that the average rate of sedimentation in all infections studied was below the normal average and differs somewhat in different conditions. The phenomenon is not influenced by the age of the patient nor by the height of the fever, and is probably dependent upon the amount of tissue destruction. Certainly in the case of tuberculous infection the resistance of the patient seems to play no part. Summing up the two papers, it may be seen that they corroborate the general feeling that in the test of the present day the rate

is not affected by gross factors such as age, sex, temperature, ingestion of food, exercise or other factors which might mitigate against the test as a clinical guide. On the other hand, the test indicates that there is something wrong with a patient, but does not by any means give any light as to what is the cause of the disturbance. If the patient is sick, this the test shows. Where, when, or how is not elucidated.

Selective Action of Roentgen Rays on the Blood Cells of the Cat.—The profound effects that radium and Roentgen ray have on the bone marrow have been proven often clinically. The severe anemia resulting from prolonged exposure to radio-active substances frequently becomes a type of aplastic anemia. WRIGHT and BULMAN (*Lancet*, 1929, ii, 217 show that the Roentgen rays have a selective action on the blood cells of the cat. If the dosage is varied, different results will take place. The important factors that are brought out are as follows: The lymphocytes are decreased early and markedly; the polymorphonuclears show an irregular initial increase with a slower and slighter degree of decrease than the lymphocytes; changes in the red blood cells occur still later; in nonfatal cases the anemia develops slowly and recovery is gradual and is paralleled by the platelet count; in fatal cases a severe acute anemia develops with evidence of hemolysis and widespread hemorrhage without the blood platelets being affected.

Effect of Coffee and Tea on Gastric Secretion.—GANTT (*J. Lab. and Clin. Med.*, 1929, **14**, 917) states that the universal use of coffee and tea as beverages among civilized people is the reason why their action should be thoroughly understood. As a matter of fact, in many European countries the main water intake is disguised as tea or coffee. For these reasons he undertook and determined the chemical reaction on the stomach of coffee and tea when taken with food. A Pavlov preparation with the experimental animal was made. The dog then had his stomach washed out, and the bread and tea mixture was introduced through the gastric fistula. As a control on the alternate days, a bread-and-water mixture, equal to that of the tea, was given. Gantt found that the chemical action of the tea and bread was practically the same as the bread-and-water. The coffee-and-bread meal produced a slightly greater amount of gastric juice the first two hours. From this investigation it seems fair to conclude that even very strong coffee and tea affect the stomach secretions only through the nervous elements of the water content, there being no, or only slight, chemical influence from the tea or coffee.

The Bacteriological Diagnosis of Whooping Cough.—SUGARE and MCLEOD (*Lancet*, 1929, ii, 165) have made an investigation of the bacteriology of whooping cough. The work of Bordet and Gengou has been looked upon with considerable skepticism, certainly until the last few years, as to whether the etiologic organism B. pertussis is responsible for pertussis. They state that in England at least no attempt has been made to corroborate or reject the findings of the two French bacteriologists. By using a French preparation, Bordet-Gengou media, they were able to isolate the organisms in 12 out of 21 cases and in all the cases examined within the first week of the disease. B. pertussis

and B. influenzæ are two distinct bacterial species, and while the latter organism was found quite frequently in the secretions from the upper respiratory tract of 50 children of ten years of age dying from other diseases than whooping cough, the B. pertussis was not found. They conclude quite definitely that the bacteriologic diagnosis of whooping cough is generally found to be easier and more exact than that of diphtheria and could be of practical service to the community.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

End Results of Surgery of the Biliary Tract.—CATTELL (*Ann. Surg.*, 1929, **89**, 930) states that cholecystectomy is the operation of choice for gall stones and for acute and chronic cholecystitis and should be done except in the very poor risk. Cholecystectomy gives relief in a high percentage of patients with gall stones. Less than 30 per cent of patients in this series having cholecystostomy have been relieved over a long period of time. The operative treatment for the noncalculous gall bladder is not satisfactory except where there is definite pathology present and conspicuous clinical symptoms associated with it. The mortality after gall-bladder operations is shown to have been appreciably increased by doing other abdominal and pelvic operations at the same time. Such practice should be discouraged. The operative mortality in patients with common duct stones is high. In addition, a considerable number operated upon for this condition have recurrence of symptoms which result in a high subsequent nonoperative mortality. The early removal of gall stones will reduce the incidence of common duct stones, and for this reason should be urged. The mortality after operation on the gall bladder alone is very low. In the past two years no death has resulted after such an operation. Two deaths have occurred in the past 275 consecutive operations on the gall bladder and ducts exclusive of malignancy and stricture. Both were in patients with common duct stones. By increasing the incidence of common duct exploration from 15 to 20 per cent of all patients, the incidence of common duct stones has been raised from 8 to 12 per cent, an increase of 50 per cent. It is obvious that exploration of the common duct should be done more frequently than is generally practised. There is a group of patients with symptoms commonly attributed to the gall bladder, whose symptoms are due to functional disturbance of the colon. Failure to obtain relief after operations for chronic cholecystitis is usually due to incomplete or wrong diagnosis.

The Determination of Preoperative Indications for Correction of Bone Deformities.—SCHWARTZ (*J. Bone and Joint Surg.*, 1929, **11**, 385) writes that the correction of fixed angular and curved deformities of

the long bones almost invariably requires a solution of continuity. Osteoclasis has been supplanted by open reduction, which makes it possible to approach these problems by methods of precision. The method described emphasizes that decisions made at the operating table relative to the level and shape of section to be made for the correction of a given deformity, are not reliable. This is true because it has been graphically demonstrated that there is only one level and section of given shape which will result in the maximum correction of a given deformity. By this method the possibility of inducing other deformities is avoided. Pre-operative determination of the level and shape of section to be removed is, therefore, necessary for the greatest assurance of the most desirable end result from operation for the correction of angular and curved deformities in long bones.

Congenital Dislocation of the Knee.—McFarland (*J. Bone and Joint Surg.*, 1929, **11**, 281) says that this rare condition has been attributed to antenatal injury, wrong pull of muscles, malposition *in utero* and primary embryonic defect. The only theories worth considering are the two last, malposition and primary defect. Both causes may operate and the cases fall into two very distinct groups, according to their etiology. Those associated with other abnormalities, such as cleft palate, hare lip, cardiac lesions and spina bifida, are due to a primary embryonic defect. Such cases are not amenable to conservative treatment and an open operation to secure a mobile knee is advisable. The second group includes the cases in which the condition is unaccompanied by other serious defects. These are due to malposition *in utero* and respond to manipulation aided, perhaps, by subcutaneous tenotomy. In the cases of long standing a difficult problem has to be attacked. It would seem likely that a tenotomy of the anterior structures of the knee and an osteotomy of the femur and flexion at the osteotomy might give a useful knee.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Diet in Diabetes.—Von Noorden (*Therap. d. Gegen.*, 1929, **70**, 241) reports on his personal experiences with different diets in diabetes. He reviews the use of some of the diets which he employed years before the introduction of insulin. He believes that the administration of

the proper diet is more difficult in the presence of insulin than it is without it. It is not correct to assume that a unit of insulin always assimilates a definite amount of carbohydrate. The patient should follow a strict diet even if the disease is present in the mildest form. The diet should be planned for each patient individually. The neglect of this principle would be as much a mistake as the failure to apply early therapy in tuberculosis and cancer. The determination of the proper diet with or without insulin is especially difficult in ambulatory patients. Cases in which synthalin proved to be a good substitute for insulin could almost always be well managed without synthalin or insulin. The beneficial effect of foreign-body therapy with the administration of proteins is so far unproven.

The Choice of Anesthesia in Operations on the Thyroid.—In the opinion of KONIG and STANHNKE (*Therap. d. Gegen.*, 1929, **70**, 250), the application of local anesthesia in patients with nontoxic goiter is preferable unless the patients are below the age of twelve years or other specific contraindications exist. On the eve preceding the operations, the patient receives 10 to 20 mg. of pantopon or "dilaudid-scopolamin." The choice of anesthesia in cases with toxic goiter is difficult. The authors appreciate the lack of unanimous opinion by leading surgeons. They, nevertheless, prefer ether narcosis in patients with toxic goiter.

The Use of Sedatives in Labor.—The important part played by sedatives in modern obstetrics is emphasized by FAIRBAIRN (*Brit. Med. J.*, 1929, i, 753). Fatigue is one of the most important factors interfering with normal delivery. Whenever, especially in the early stage of labor, the woman is worried and fatigued, and there are signs of irregular uterine contractions, a liberal dose of some sedative should be given and repeated if necessary. Morphin in doses of $\frac{1}{4}$ to $\frac{1}{3}$ grain may result in beneficial effect. The purpose of morphin-hyoscin narcosis is not analgesia or anesthesia, but amnesia. The successful induction of amnesic narcosis removes almost entirely the inhibitions of uterine action of emotional and psychic origin. It also lessens the fatigue. Reflex response to stimuli augmenting the strength of contractions may be diminished under this narcosis. It should be limited, therefore, to cases in which the exclusion of fatigue and inhibitory influences plays a more important rôle than the decreased reflex response. The "twilight sleep" should be given soon after rhythmical labor pains are definitely established, provided the patient is "prepared." The patient should be isolated from noise and light. An initial dose of $\frac{1}{4}$ grain of morphin with $\frac{1}{150}$ grain of hyoscin should be given, followed at hourly intervals by $\frac{1}{450}$ grain of hyoscin. In general, the standard dose should be increased in first labors, for big women of strong physique, and for imaginative, oversensitive and nervous patients. Idiosyncrasies for hyoscin must be watched for. A memory test should be applied to determine the state of amnesia. Flushing of face and dilatation of pupils are not necessarily indications of overdosage. With overdosage of hyoscin, the pulse rate shows marked rise and the respirations a marked fall. If the patient is unable to empty her bladder, a catheter should be used. Important is the continuous observation of the patient

by a skilled nurse. In the second stage of labor there may be indications for falling back on a light general anesthesia, especially once the outlet begins to gape, and birth is imminent. Sedatives should be given to patients in whom a long and tedious labor may be anticipated. The problem of relief of pain of labor and the saving of nervous strain without interfering with the normal function of delivery is still unsolved.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Typhoid Fever in Children.—HALPERN (*Am. J. Dis. Child.*, 1929, **38**, 10) studied 67 children ill with typhoid fever, with an age range of from ten months to twelve years. He noted that the onset was relatively abrupt in almost one-half of the cases. Abdominal pain was a frequent initial complaint, and because of its location at times in the right lower quadrant and the sudden onset with vomiting it occasionally made difficult the exclusion of acute appendicitis. Signs of meningeal irritation were relatively frequent, and often the disease with this complication simulated the picture of a true primary meningitis. The pulse rate was rapid and in proportion to the degree of the fever in one-fourth of the cases. The blood in 6 per cent of the cases showed a leukocytosis in the absence of complications instead of the usual leukopenia. Positive Widal reactions outnumbered the positive blood cultures and both were more frequently obtained during the second week of the illness. The stools gave a higher percentage of positive cultures than the urine. The complications were usually suppurative processes. Death occurred most often in the second week of the illness. Signs of meningeal involvement often preceded death.

Comparative Effects of Diphtheria Toxoid and Toxin-antitoxin as Immunizing Agents.—WEINFIELD and COPPERSTOCK (*Am. J. Dis. Child.*, 1929, **38**, 35) record their experiences with toxoid in the active immunization against diphtheria. In a well controlled group of 104 adults with positive reactions to the Schick test, it was found that in 83 or 92 per cent of 89 that were treated with two doses of 1 cc. each of toxoid, the reaction became negative. Of 15 persons receiving one dose of 1 cc. of toxoid, the Schick reaction was also rendered negative in 7 or 46 per cent. In the routine employment of the Schick test, certain sources of error were noted. The majority of the subjects comprising this series came from rural districts. A high incidence of positive reactions to the Schick test, 73 per cent was found in this group, and this high incidence stands in interesting contrast to the low proportion of

persons susceptible to diphtheria found in well populated areas. The interesting phenomenon of reactions to the administration of toxoid was studied. While in a general way it was found that local reactions to toxoid were much less frequent as compared with those following toxin-antitoxin, general reactions to toxoid were observed with greater frequency. It was noted that both local and general reactions to toxoid were rare in children. Studies on the nature of these reactions to the toxoid tend to indicate that allergy plays an important part in their manifestations. The high incidence of reactions to toxoid in persons presenting both a history of allergy and a pseudoreaction to the Schick test was particularly striking. The use of antitoxin entails the possibility of the production of sensitization to horse serum, whereas with the use of toxoid this possibility is obviated. The authors feel from their experience that toxin-antitoxin is inferior as an immunizing agent to toxoid. The relatively greater stability, innocuousness, and need for fewer injections of toxoid are additional advantages.

Congenital Pyloric Obstruction.—Moore, Brodie, Dennis and Hope (*Arch. Ped.*, 1929, **46**, 416) remind us that congenital pyloric obstruction has shown a very rapid increase in the past forty years. The statistics show that 2.7 per cent of all infants under one year of age suffer from this disease. Dietary habits may be responsible for this increase as well as its occurrence in several members of the same family and in twins. Variations in diet may also explain the seasonal incidence and geographical distribution. The diet of the average American mother is normally very low in vitamin B, although she needs during pregnancy and lactation for the protection of her infant three or four times the amount of this factor that she does for her own well being. The authors in their laboratory by means of a deficiency of the vitamin B complex in the maternal diet produced pyloric obstruction in young rats. Other phases of the deficiency found in the same individuals or litter mates were hemorrhage and polyneuritis. In the animals thus affected the motor nerves to the pyloric region showed myelin degeneration, which is the typical pathology of a vitamin-B deficiency. This experimental work gives a basis for the prevailing theory that pylorospasm results from unbalance of the autonomic nervous system. Vitamin-B deficiency as produced experimentally and found clinically in beriberi occurs most commonly in males. In clinical pyloric stenosis from 75 to 90 per cent of the cases are found in boys, and this experimental series showed 87.5 per cent of males. Clinical experience bears out the experimental evidence of the association of pyloric obstruction with hypertonicity and hemorrhage. A subnormal temperature and cold extremities in premature or malnourished infants are often the first signs of a vitamin-B deficiency. As prophylactic for pyloric obstruction and other manifestations of a dietary deficient in the vitamin-B complex, every woman should receive desiccated yeast throughout pregnancy and lactation. The baby should also receive it from the beginning. After symptoms of pyloric obstruction have become manifest, treatment should include the usual atropin and thick cereal and also desiccated yeast. In serious cases blood transfusion is indicated.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

R. L. GILMAN, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Untoward Reactions following Toxin Treatment for Dermatitis Venenata.—TEMPLETON (*Arch. Derm. and Syph.*, 1929, **20**, 83) reports five illustrative cases of an hitherto undescribed reaction to the administration of specific rhus antigen for poison oak dermatitis. The reaction may be either a localized urticaria at the site of injection of the extract or a generalized eruption may appear, composed of urticarial wheals and papulovesicles of dermatitis venenata. The pruritus is severe and hospitalization is frequently necessary. Either reaction may begin from twenty-four to seventy-two hours after the injection. The patient may or may not have had an allergic history. The writer believes that the patient is sensitized to the extract of poison oak by the disease itself, and that the patient reacts allergically to the injection of the specific antigen employed. To prevent these reactions, the writer has used gradual desensitizing measures by the use of small initial doses. Since the abandonment of the orthodox larger doses no further untoward reactions have been noted and the therapeutic results have been equally satisfactory.

Bismuth is Absorbed.—BOYD (*J. Am. Med. Assn.*, 1929, **93**, 269) using potassium bismuth tartrate in oil believes the drug is absorbed satisfactorily intramuscularly, provided the dose is decreased and the interval shortened, that is, a dose of 0.1 gm. every three to five days, and that a scrupulous technique is employed, changing to a water-filled needle after the drug has been aspirated into the syringe. The injection is given slowly. Massage is extremely important, both immediately following the injection and with frequent massage at intervals throughout the course of the injections. Roentgenograms are used to check the absorption of bismuth. Eleven illustrative cases are reported.

The Chlorid Content of the Whole Blood in Eczema.—BURGESS (*Arch. Derm. and Syph.*, 1929, **20**, 69) reviews the literature on whole blood chlorid studies and quotes Myers' normal figures as ranging from 450 to 500 mg. of sodium chlorid per 100 cc. of whole blood with lower figures as still within normal limits. The author did chlorid determinations on 5 normal individuals, obtaining a range from 429 to 462 mg. In a group of various dermatoses (acne, pemphigus and generalized pruritus) the determinations ranged from 413 to 492 mg.

In a series of 20 cases eczema (various types and clinical varieties) the chlorid range was from 426 to 495 mg. All of these results were in normal limits and high or low values could not be correlated with any clinical classification of eczema. The author points out that his finding demonstrate no abnormality in chlorid metabolism in eczema or other dermatoses investigated and that there is no rationale for attempting to reduce the chlorid content of the tissues by a salt-free diet or aiding chlorid elimination. Any satisfactory results obtained by the intravenous administration of sodium thiosulphate in eczema appears to depend on factors other than the alteration of the blood chlorids.

Incidence of Foot Ringworm among College Students.—LEGGE, BONAR and TEMPLETON (*J. Am. Med. Assn.*, 1929, **93**, 170) have made a survey on the incidence of ringworm of the feet in college students. They found the incidence in new men students to be 53.3 per cent and 15.3 per cent in women students. At the end of a year of physical education and gymnasium work they found the rate in men students raised to 78.6 per cent, while the women showed but a slight increase, that is, to 17.3 per cent. The observers believe the discrepancy in the increase of incidence between the men and women students (25.3 per cent as against 2 per cent) to be accounted for by the superior sanitary conditions obtaining in the new women's gymnasium. They point out that in addition the women would acquire less ringworm of the feet due to cleaner habits, a higher type of hygiene and lighter footwear. Emphasis is laid on the precaution of always wearing some sort of foot covering in the gymnasium, swimming pool runways and showers.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Intestinal Obstruction following Baldy-Webster Operation.—For many years one of the theoretical objections to the Gilliam type of operation for the correction of retroversion of the uterus has been the possibility of the occurrence of a subsequent intestinal obstruction due to a loop of small bowel being caught in one of the open spaces between the round ligaments and the abdominal wall. Such a possibility has seldom been considered following the Baldy-Webster operation, but the case reported by PEMBERTON and SAGER (*Surg. Clin. North America*,

February, 1929, p. 203) demonstrates that it can happen. In this case, in less than four weeks after a Baldy-Webster operation had been performed an acute intestinal obstruction developed, due to a loop of small bowel herniating from behind forward through the opening in the broad ligament through which the round ligament had been pulled in order to attach it to the posterior surface of the uterus. In another case which they report, although no obstruction developed, it was noted that as the result of a Baldy-Webster operation having been performed some twelve years previously there was an opening in each broad ligament at the site of the round ligament perforation large enough to admit two fingers which were certainly sites of potential internal intestinal strangulation. In order to prevent the occurrence of such a condition, they call attention to a point which Webster described in his original description of the operation and caution that it should always be observed, namely, that each round ligament should be stitched to the edges of the opening in the broad ligament through which it is pulled. This little point in the technique is probably frequently omitted, but its observance will most likely preclude the subsequent stretching of these small openings with the accompanying possibility of a life-threatening acute intestinal obstruction.

Primary Epithelioma of the Vulva.—A series of 71 cases of primary epithelioma of the vulva observed at the Mayo Clinic between 1907 and 1927 has been reported by RENTSCHLER (*Ann. Surg.*, 1929, **89**, 709), who states that it is a rare disease, being 25 times less frequent than carcinoma of the cervix. Pruritus must be considered as a significant etiologic factor since 40 per cent of the patients gave a definite history of preëxisting pruritus. The most common symptom is itching. Ulceration may appear any time during the course of the disease and 47.5 per cent of the patients had ulceration when first examined. This is associated with pain, more or less discharge and at times with slight bleeding, then follows insomnia, secondary anemia, cachexia and not infrequently urinary complaints. A biopsy will differentiate the condition from metastatic growths, tuberculosis and syphilis when there is doubt as to the diagnosis. The local lesion may be of the superficial vegetative type or it may be of the deep infiltrative type. Metastasis may occur at any time during the course of the disease. The lymphatic drainage, with the exception of that of the clitoris, is first to the inguinal lymph nodes, usually on the same side, but drainage to the opposite side is anatomically possible and not infrequent. The lymphatic drainage from the clitoris is usually directed into the pelvis; similarly the inguinal lymph nodes drain directly into the pelvis. The regional lymph nodes may be palpable without containing malignant cells and conversely the nodes may contain malignant cells without being palpable. Therefore, the only way to be sure whether or not they contain malignant cells is to remove them and to study them histologically. Wide excision of the local growth and excision of the superficial and deep inguinal nodes on both sides, whether enlarged or not supplemented by radium and Roentgen ray treatment is the treatment of choice unless metastasis obviously has advanced beyond the point where surgical intervention can help the patient or unless the existing growth is of the third or fourth grade of malignancy, according to Broders' classification.

In these cases of grave malignancy it would seem wiser to excise only the local growth and supplement this by radium and Roentgen rays applied over the site of the original growth and the lymphatic drainage. In those cases in which there is obvious lymphatic involvement and a grave malignancy, radium and Roentgen rays alone should constitute the treatment because in these cases the recurrence is too prompt to warrant surgical procedures. Forty-five of the patients in this series are dead, all except one dying from carcinoma. The remaining 17 patients who are still living include 13 who are free from recurrence after an average duration of 7.77 years. One patient had a recurrence after eight years, 1 after four years and 1 within less than a year after operation. Therefore, the prognosis is fair for prolongation of life but poor for cure and would seem to be in direct proportion to the grade of malignancy.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

The Use of Ultraviolet Rays in Diseases of the Nose and Throat.—The biologic action of light is due primarily to photochemical reaction. Waves of light are absorbed by living cells and produce photobiochemical reactions which influence the whole organism. All living cells are sensitive to the ultraviolet rays from 3100 to 2500 Angström units, which penetrate to the superficial layers of the living epidermal cells, producing at the site of irradiation an erythema characterized by hyperemia, leukocytic infiltration and an intradermal edema due to transudation of fluids and exudation of plasma. On the theory that at the site of irradiation there is produced a bactericidal substance which is distributed throughout the body by the circulatory system, EIDINOW (*J. Laryngol. and Otol.*, 1929, **44**, 177) has adopted a special technique of general treatment, using a quartz mercury-vapor lamp which emits ultraviolet rays shorter than 2970 Angström units. Irradiation of approximately one-sixth of the body surface is conducted two to three times a week, but an interval of from ten to fourteen days is allowed between exposures of any given cutaneous area. He reports that "early cases of lupus of the skin, nasopharynx, palate and larynx have been healed by these means." Eidinow states that a direct bactericidal action from ultraviolet irradiation is an erroneous impression, inasmuch as serum and lymph greatly impede the penetration of the bactericidal rays, while excessive dosage produces extensive edema and necrosis. Careful dosage in local treatment, however, hastens the repair of many types of septic wounds. As the normal mucous membrane is about three times as sensitive as normal white skin to light, the dosage must be regulated with great care. He believes that the use of quartz rods, applicators and mirrors to transmit or reflect the light to the site of

infection is unsatisfactory, due to the reduction in intensity of radiation. The author concludes by mentioning that further research on treatment by means of sensitizers and ultraviolet radiations emitted by high-frequency current are in progress.

Irradiation from Quartz Mercury-vapor Lamp as Factor in Control of Common Colds.—By exposing a group of individuals, who were susceptible to the "common cold," to the irradiations of an ordinary quartz mercury-vapor lamp once a week for a period of from ten to eighteen minutes (dividing the time of exposure equally to the front and back of the naked body) at a distance of 30 inches, MAUGHAN and SMILEY (*Am. J. Hygiene*, 1929, **9**, 466) found that as a rule the incidence of colds was reduced by at least 40 per cent. The treatment was carried out during the dark months of the year, when fewer solar ultraviolet rays are available. Inasmuch as the absence of ultraviolet radiation constitutes only one of several recognized factors capable of reducing general resistance to acute respiratory infection, it is not to be expected that the supplying of this deficiency will prevent the occurrence of all cases of "common colds." However, the authors believe that their results indicate a justification for the employment of ultraviolet therapy at weekly intervals in those persons showing a marked tendency to recurrent head colds.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Natural Heliotherapy.—Present day theory, says GOTTLIEB (*Arch. Physical Therapy, Roentgen Ray, Radium*, 1929, **10**, 110), recognizes that every chemical reaction is started by radiant energy. The living animal absorbs stored up sun energy in the form of food, which, in itself or in its original form, the sun ray, excites the living organism to activity accompanied by setting free stored up energy. This latter is expressed in greater viability, body and mental activity. Whenever body energy is deficient, heliotherapy finds its indications. The value of sun radiation has been proved in rickets, osteomalacia and delayed union of fractures. It is beneficial in localized wounds, ulcerations due to circulatory or neurotrophic disturbances, and infected wounds. Chronic osteomyelitis, chronic arthritis and syphilis refractory to treatment are favorably influenced. Besides tuberculous bone and joint affections, heliotherapy is indicated in deficiency diseases of the

type of Osgood-Schlatter, Legg-Perthe, Freiberg, Koehler and other conditions classed as osteochondritis.

Proper effects are obtained only by proper dosage. Overstimulation is likely to occur unless the treatment is individualized and supervised. It should be commenced with air baths daily for five minutes, increasing the time until tolerance for the temperature of the air is created. Only then should the sun rays be introduced, beginning with small doses and slowly increasing to the maximum of tolerance, which varies considerably.

Colonic Diverticula.—CASE (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 207) observes that diverticulosis of the colon is a symptomless condition commonly met with at roentgenologic examination. Diverticulitis, which is an inflammatory reaction to diverticulosis, is also commonly encountered, the inflammatory sequels manifesting themselves in various ways so that cases may be clinically classified as of the enterospasm type, the hyperplastic type and the pseudo-appendicitis type. When enterospasm predominates there are the ordinary signs of chronic colitis with no indications of tumor or obstruction. In this type a sudden development of acute symptoms may suggest a left-sided appendicitis. In the hyperplastic, obstructive type the symptoms are those of long standing constipation, colicky pains and usually a palpable tumor. For the roentgenologic examination Case feels that both the opaque meal and enema are necessary. The roentgenologic differential diagnosis involves sigmoiditis, hyperplastic tuberculosis, actinomycosis, syphilis, and, most especially, carcinoma. No case of supposed carcinoma of the lower bowel should be regarded as inoperable either before or during laparotomy until the question of diverticulitis has been considered and if possible settled.

Iodized Oil and Pneumoperitoneum in Roentgen Gynecologic Diagnosis.—As a result of increased experience, STEIN and ARENS (*Radiology*, 1929, **12**, 341) have become more cautious in the diagnosis of tubal obstruction, and consider spasm to be a definite and frequent phenomenon in normal pelvic viscera. They feel that spasm as exhibited in the uterus and tubal isthmus is comparable to spasm observed in other hollow viscera, and is a defense reaction against the introduction of a foreign substance or against distention. This phenomenon accounts readily for the numerous cases in which they found apparent obstruction, in which gas alone was used for testing tubal patency, and in which on repeated tests the tubes proved to be patent. This was graphically illustrated when iodized oil was utilized showing one or both tubes patent immediately following the usual patency test with gas in which the tubes appeared to be obstructed. The converse has also been observed, namely, that after a satisfactory patency test with gas the instillation of iodized oil yielded a typical picture of cornual or isthmic obstruction. Again, one tube has appeared filled and the other empty. The experience of the authors emphasizes the necessity for repeated patency tests when obstruction is encountered, especially in the absence of obvious inflammatory lesions.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Mental Hygiene and the Practice of Medicine.—STRECKER (*Mental Hygiene*, 1929, **13**, 343) believes that psychiatry has much to offer the general practitioner. He considers that in every person who is sick there is an unknown factor representing his peculiar reaction as an individual. Since psychiatry has methods to impart that make it possible and feasible to recognize and handle this factor, it would be valuable to anyone treating patients. The objections to psychiatry, he believes to be founded on misconceptions. While it is necessary and desirable to place mental patients in special hospitals, this is also true of almost all of the specialties. The objection that treatment of mental patients is individualized and can have no application in other fields he holds to be erroneous on the grounds that it has a wide range of usefulness. The adoption of hydrotherapy, occupational therapy, and so forth, in general medical practice, he gives as examples of such application. Statements that the etiology is unknown in psychiatry he meets by showing that in many instances the etiology is quite definitely known and that in the obscure instances the psychiatrist is no worse off than are those who treat cancer, and so forth. As to legal entanglements he contends that these are no more prevalent in psychiatry than they are in other specialties. On the other hand, he believes that any failure to take psychiatric conceptions into the field of medicine impairs the efficiency of the physician. The occurrence of mental symptoms in relation to typhoid fever, encephalitis, goiter, and so forth, make some understanding of psychiatry and psychiatric therapy essential. The mere handling of a patient prior to an operation, he believes, may make the difference between a successful and an unsuccessful procedure. During convalescence from any serious illness he believes the problem to be primarily psychiatric in nature and that many cases, if handled properly, can be prevented from arising too soon and thereby causing a relapse, or from falling so deeply in love with their illness that they remain chronic invalids. During the acute life periods again psychiatry is invaluable. Since 70 per cent of the daily contacts of physicians are made up of functional and not organic pathology, the author believes that the physician should handle functional disease in all of its aspects, only resorting to the specialist for cases which are beyond his scope. He gives a general plan of treatment in these cases.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D.,
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Tuberculous Cervical Adenitis.—MILLER and SHEDDEN (*Am. Rev. Tuberc.*, 1929, **19**, 511) discuss the present status of the problem of tuberculous cervical adenitis and indicate that the localization of this infection does not constitute an individual disease, but that it is probably associated with foci elsewhere. They tend to agree with Krause that tuberculosis is a constitutional or diffuse infection resembling syphilis, with numerous loci, but with few manifest foci of anatomic change. The authors have studied a series of cases of tuberculous cervical adenitis, and find that in the early stages of its existence free tubercle bacilli may be disseminated, resulting in a mild bacteremia. Thus distant as well as local tuberculous processes are developed. The condition lends itself to general treatment, and surgery is to be considered only when other measures have failed.

Skin Hypersensitiveness in Rheumatic Fever.—The problem of the cause of rheumatic fever is far from being settled. It has been suggested that the disease is an allergic phenomenon and many attempts have been made to discover a specific allergin. BIRKHAUG (*J. Infect. Dis.*, 1929, **44**, 363) in a report on skin tests performed in European clinics with filtrates, autolysates and bacterial suspensions of nonmethemoglobin-forming streptococcus, Streptococcus viridans and hemolytic streptococcus, considered that a nonspecific, common allergenic factor is present excessively in the bacterial products of indifferent and viridans streptococci and moderately present in the solutions of hemolytic streptococci, to which, cases with either acute rheumatic infections or chronic infectious arthritides, react hyperergically. Since tuberculosis is the typical example of allergy it is of interest that REITTER (*Wien. klin. Wchnschr.*, 1928, **41**, 473) found four-fifths of persons with acute articular rheumatism to give distinct allergic reactions after intracutaneous tuberculin and he hypothesized that it is only in such hypersensitive persons the symptom complex of acute articular rheumatism develops. WILKINSON (*Brit. Med. J.*, 1928, i, 749) also believed that the symptom complex hitherto associated with "rheumatism" may be the effect of tuberculosis and advocated the use of tuberculin in detecting the variety of lesions which occur in the early stages of chronic tuberculosis. Thus it is seen that the ill-defined symptoms under the term "rheumatism" are still open to different interpretations and the ideas on the subject are still in a state of flux.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE. WASHINGTON, D. C.

Immunologic Studies of Typhoid Vaccination by Mouth: I. Agglutinins Formed in Persons Treated Orally with Triple Typhoid Bacterin.—A new interest in the phenomena of local immunity has been stimulated by the recent work of Besredka. The evidence for oral immunization against the typhoidal fevers has largely been based on clinical data. To determine a possible experimental foundation for such clinical claims, HOFFSTADT and THOMPSON (*Am. J. Hyg.*, 1929, **9**, 1) undertook the present study. Of the 134 persons treated orally with with the triple typhoid bacterin (98 with the liquid bacterin and 36 with the typhoid capsule), 87.7 per cent gave positive agglutinins for typhoids. Of the 74 persons who were tested for complement fixations, 83.5 per cent gave positive reactions. This agrees with the results reported for the subcutaneously inoculated individuals. A slightly higher percentage of the group treated with liquid bacterin gave positive reactions than the capsule-treated individuals. The percentages positive of the bile-treated persons were higher than those not treated with bile. In the bile-prepared group which was treated with liquid bacterin the titers for agglutinins were higher than in any other group. The bile was given in those cases before the administration of the bacterin. It appears, therefore, that it may be better to separate the bile from the bacterin and give it before the first dose rather than simultaneously with all three doses of the bacterin. From these results the authors conclude that agglutinins, and complement fixations can be produced by oral inoculation of individuals with triple typhoid bacterin in the dry form as a capsule. There is no delay in the appearance of the agglutinations or complement-fixation reactions over that which was found in the liquid triple bacterin method. Neither antibody is consistently present in the immune person.

The Transfer of Tuberculosis by Dust and Other Agents.—AUGUSTINE (*J. Prev. Med.*, 1929, **3**, 121) made tests to determine the presence of tubercle bacilli: (1) In the air in the rooms of tuberculous persons; (2) in the dust upon surfaces in their rooms; (3) in the dust removable from their clothing; (4) in the washings from the hands of children living in their homes. The experiments were made in the houses of families of which one or more members had tuberculosis with sputum positive for tubercle bacilli. The evidence collected suggests that

the demonstration of virulent tubercle bacilli in dust collected from the rooms or clothing of patients with open tuberculosis may be used as a measure of the danger to which those in contact with the patient are subjected. Dust from the rooms or clothing of patients who keep themselves clean contain tubercle bacilli much less frequently than dust from uncleanly homes and people. Tubercle bacilli are recovered more frequently from the rooms of women than of men with open tuberculosis, and less frequently from the clothing of women than of men. These relations may be explained by the greater personal cleanliness of women and their inability, when ill, to keep their houses clean. Tubercle bacilli are recovered more frequently from the homes and clothing of colored than of white patients. The number of tubercle bacilli in the sputum of the patient is a factor in determining the presence or absence of tubercle bacilli in surrounding dust. The author's data cannot be used to determine the relation of infected dust to human infection because most of the families studied had long been exposed to open tuberculosis. To determine whether tubercle bacilli in the dust of houses infect members of the household it would be necessary to continue observations similar to those reported over a period of years in order to discover the frequency with which latent and manifest tuberculosis make their appearance in those who have been exposed to infected dust.

Detoxifying, Diffusing, Germicidal and Surface Tension Depressing Properties of Soaps.—DAVISON (*J. Infect. Dis.*, 1928, **43**, 292) prepared twelve common soaps and studied their detoxifying, diffusing, germicidal and surface tension depressing properties. He states that soaps possessing high detoxifying ability diffuse readily, are highly germicidal, but are correspondingly ineffective surface tension depressants.

Correction.—On page 437 of the September issue, the reference to Yates' article should be to the J. Laryngol. and Otol., 1928, **43**, 852, and not to the Arch. Otolaryngol, as would be inferred.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL will be translated at its expense.